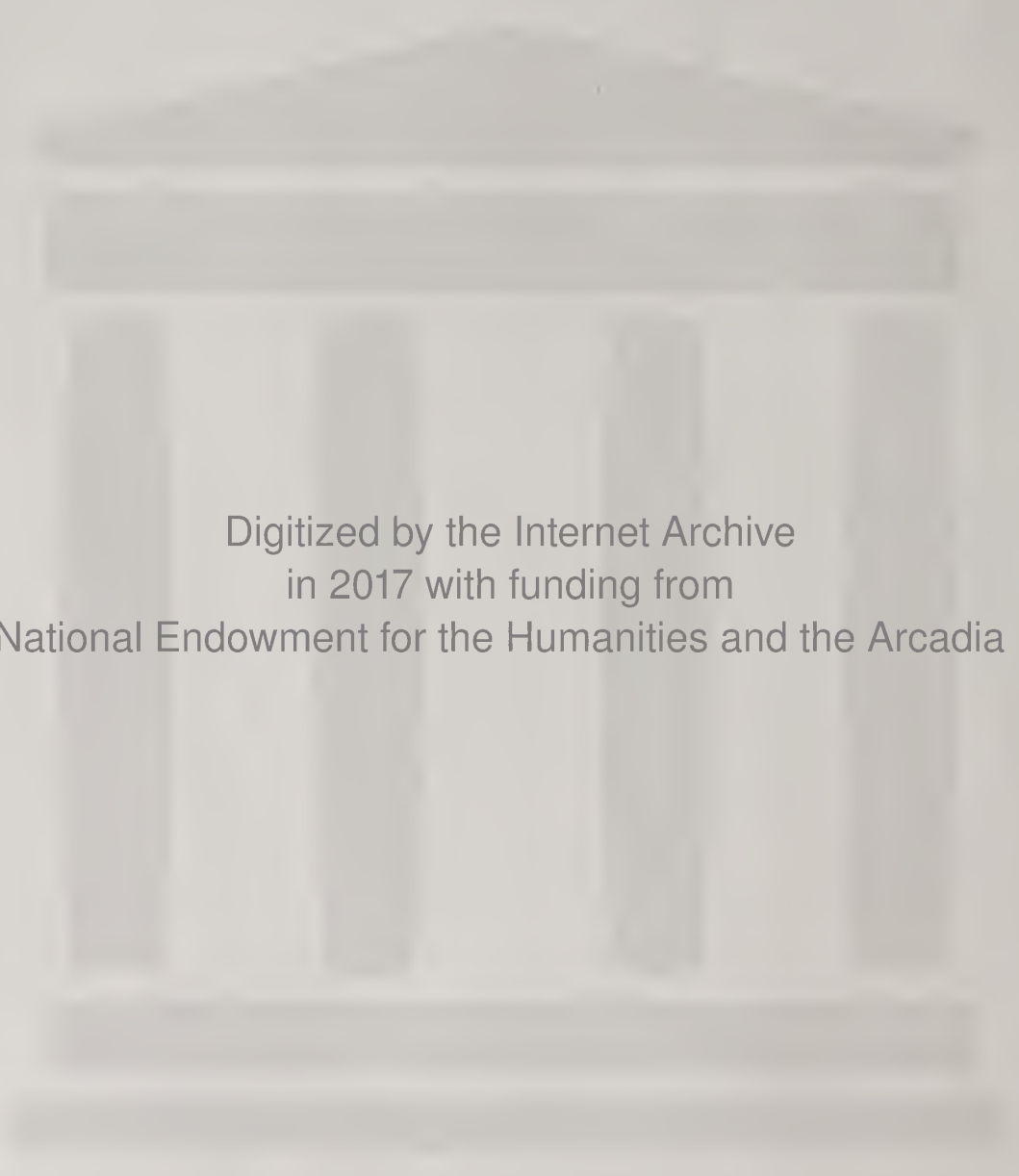


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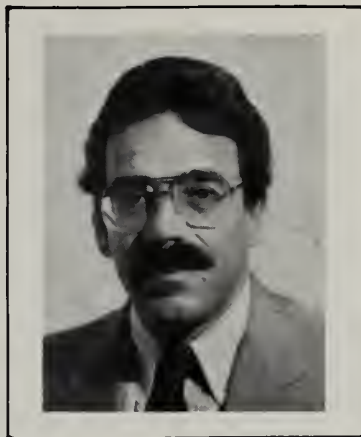
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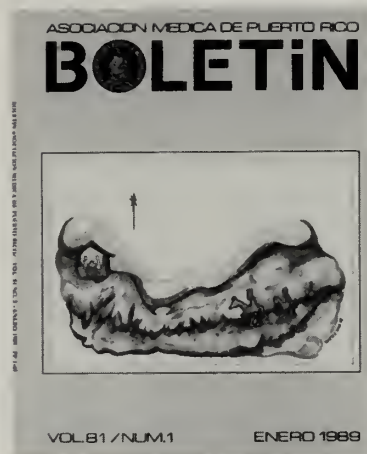
En este primer número de 1989 ofrecemos a nuestros lectores la oportunidad de obtener créditos en Educación Médica Continuada (Categoría I) al devolver contestadas una serie de preguntas relacionadas a uno de los artículos del número. Esto se ofrecerá cada dos meses y al final del año aquellos que cumplan los requisitos recibirán un certificado por 6 créditos. El procedimiento es sencillo y los detalles se describen en la hoja de respuestas. Este ha sido uno de los objetivos de la Junta Editora por largo tiempo y logrado luego de cumplir con un proceso burocrático extenso y en ocasiones decepcionante. Al final prevaleció el sentido común y podremos ofrecerle algo más para el beneficio de nuestros lectores.

Aparece además el primer trabajo de la serie "Mirada a Nuestro Pasado", como anunciamos en el número de noviembre de 1988. Además del artículo original publicado hace 50 años en nuestra revista le sigue un análisis excelente del trabajo, donde se analiza el artículo desde la perspectiva de hace medio siglo y la actual.

"Dilemas en la Práctica de la Medicina para el Siglo XXI" es otra serie nueva sobre un ciclo de conferencias que auspicia el Departamento de Medicina de Familia de la Escuela de Medicina de la Universidad de Puerto Rico y que serán publicadas en el Boletín durante el presente año. La Junta Editora agradece al Dr. Anibal Marín su valiosa cooperación, haciendo posible la publicación de estas conferencias para beneficio de aquellos compañeros que no pueden asistir a las mismas.

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico para el 1989 confía poder continuar ofreciendo a sus lectores una publicación de contenido amplio, amena lectura y la calidad científica que nuestra clase médica merece. Vamos a poner menos energía en evaluar lo que hemos hecho y más en estimular lo que somos capaces de lograr.

Rafael Villavicencio, MD, FACC
Presidente, Junta Editora
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Nuestra Portada

Los Reyes Magos, acuarela de la artista puertorriqueña Beatriz I. Vega Meléndez. Nacida en San Juan Puerto Rico, es joven estudiante del cuarto año de la Facultad de Humanidades de la Universidad de Puerto Rico, donde concentra sus estudios en Artes Plásticas.

El diseño de la portada es una muestra de una serie de tarjetas de Navidad pintadas en acuarela, en las que se armonizan el motivo religioso de la época con los aspectos más criollos de nuestra tradición.

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico agradece a la artista y a su padre, el Dr. Luis A. Vega-Rodríguez su colaboración para hacer posible la publicación de su obra en nuestra portada.



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Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

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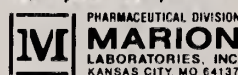
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1. Eliakim R, Ophir M, Rachmilewitz D. *J Clin Gastroenterol* 1987;9(4):395-399.

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The Medical Treatment of Congestive Heart Failure

Edgardo Hernández López, MD, FACC

The management of patients with congestive heart failure (CHF) has changed dramatically in the last decade. Recent advances in our understanding of its pathophysiology have lead to new insights into the diagnosis, evaluation and particularly the management of this syndrome. The recent demonstration that vasodilator therapy prolongs the life^{1, 2, 3} of some of these patients has changed the traditional approach to their treatment. A wide variety of therapeutic options are now available to the clinician and these have begun to challenge the most time-honored approaches to the treatment of this condition. In the past we believed that systemic perfusion pressure had to be supported to preserve organ function; we now routinely lower blood pressure in these patients with potent vasodilator drugs. We also thought that the administration of digitalis was an essential part of any successful therapeutic regimen for congestive heart failure;⁴ nowadays the benefits of chronic inotropic stimulation are questioned and even thought to be detrimental by some.⁵ The use of cardiodepressants drugs (i.e., beta-blockers) has been suggested by others.⁶

In this review we will attempt to bring some of these issues into perspective. Special attention will be given to recent developments in the elucidation of the underlying pathophysiologic mechanisms of this syndrome as they apply to the rationale of therapy.

Pathophysiologic Mechanisms of Congestive Heart Failure

Congestive heart failure is a clinical syndrome characterized by dyspnea, fatigue and edema, which most commonly result from pathophysiologic events that follow a severe insult to left ventricular function. Although diastolic dysfunction may play an important, and at times, preponderant, role in many patients, it is usually related to a marked impairment of systolic performance, which is caused by ischemic or cardiomyopathic processes. Prolonged pressure or volume overload of the heart (conse-

quent to long-standing valvular stenosis or insufficiency) may also lead to myocardial dysfunction, either because of an increased left ventricular wall stress, a decrease in the intrinsic contractile state of the myocardium, or both.

The hemodynamic hallmarks of the heart failure state are a decrease in cardiac output and an increase in right and left ventricular filling pressures. Several compensatory mechanisms are intrinsically available to the circulation to maintain cardiovascular homeostasis in patients with CHF, but the concept currently prevailing is that these compensatory mechanisms may cause detrimental effects if they are exaggerated or sustained for long periods. Congestive heart failure is now viewed as a syndrome in which the activation of a number of neurohumoral systems ultimately impede ejection and further impair left ventricular function, leading to a vicious cycle (figure 1). A very important issue, not yet clearly defined, is the relative role of each one of these mechanisms at different stages of the syndrome. Bayliss

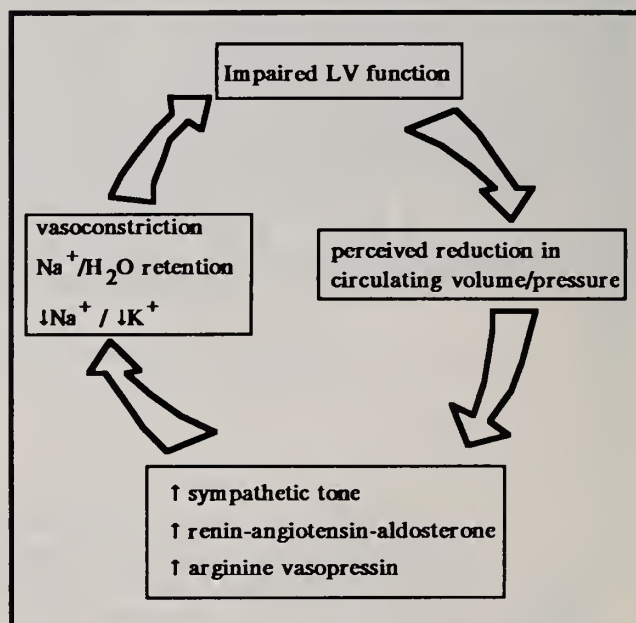


Figure 1. Congestive heart failure activates a number of neuro-humoral systems that ultimately impede ejection and further impair left ventricular function, leading to a vicious cycle.

From the Cardiology Section, San Juan VA Medical Center and the University of Puerto Rico School of Medicine.

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has suggested that the earliest neuroendocrine response to heart failure is activation of the sympathetic system alone.⁷ This may have a crucial importance on the determination of the most appropriate form of therapy at a given time in the evolution of the disease.

An understanding of the pathophysiology of congestive heart failure is essential for the development of appropriate therapeutic guidelines for its treatment. Following is a review of the most recent concepts about the pathophysiologic mechanisms underlying the perpetuation and progression of this syndrome.

A. Cellular mechanisms

There is substantial, although not yet conclusive evidence that the failing heart is in an energy-depleted state. Biochemical and morphometric studies of the hypertrophied heart suggest that this is the case.⁸ Parallel biochemical⁹ and morphologic¹⁰ studies of the development of hypertrophy in the pressure-overloaded rat heart have demonstrated that the development of myocardial hypertrophy is associated with an increase in the fraction of cell volume occupied by energy-consuming myofibrils, whereas the mass of mitochondria, which regenerates adenosine triphosphate (ATP), decreases. After long standing aortic constriction in rats, the volume fraction of the cardiac myocyte occupied by myofibrils increased to a greater extent than mitochondrial volume.¹¹ Thus, both relative ischemia and a disproportionate increase in the content of contractile proteins relative to the content of mitochondria could contribute to a deficit of chemical energy in the failing heart. Evidence has been provided that the increased energy demands of the failing human heart are met by increased oxygen extraction rather than increased coronary flow.¹²

Decreased myocardial high-energy phosphate contents have been observed in animal models of heart failure after pressure overloading of the left¹³ and right¹⁴ ventricles, and endomyocardial biopsies in human hearts have shown a correlation between decreased ATP content and impaired function.¹⁵

Verification of the hypothesis that the failing heart is energy depleted would be of considerable importance to our understanding of the pathogenesis of CHF. The possibility that an energy deficit contribute to the spontaneous deterioration that occurs in the chronically overloaded myocardium is of the greatest theoretical significance. The final stage in the response of the heart to a chronic overload —myocardial cell death with replacement of myocardial contractile elements by fibrous tissue— may be explained in part by inadequate delivery of chemical energy needed to sustain the high levels of mechanical work. In addition, further understanding of the energetics of the failing heart will be of considerable importance in the formulation of a rationale approach to therapy. For instance, drugs that increase energy expenditures, may be expected to worsen cell damage, exacerbate relaxation abnormalities and promote arrhythmias. Conversely, therapy that improves the balance between energy delivery and energy expenditure might be expected to improve prognosis in CHF.

B. Neuroendocrine factors

Activation of the sympathetic nervous system¹⁶ and the angiotensin-aldosterone system¹⁷ and release of arginine vasopressin (AVP)¹⁸ are known to occur in patients with heart failure. It is widely assumed, although not proven, that these systems are activated in response to a perceived sense of ineffective circulating volume.¹⁹ The precise signal that activates these compensatory responses in heart failure is not known nor is it known where these signals are processed. It is quite likely, however, that heightened sympathetic drive²⁰ and increased angiotensin-aldosterone levels²¹ contribute importantly to the clinical expression of the syndrome. In addition to activation of systems designed to constrict blood vessels peripherally and retain salt and water, heart failure is now known to be characterized by the release of a series of endogenous vasodilator natriuretic substances, including atrial natriuretic factor (ANF),²² certain prostaglandins^{23, 24} and dopamine.²⁴ A brief review of the neuroendocrine disturbances that have been described in heart failure follows.

1. Baroreceptor function

Sensory receptors in the heart, lungs, and great vessels, termed baroreceptors, modulate neurohumoral activation to maintain blood pressure and volume status during changes in posture. These receptors mediate the vascular and sodium retentive response to volume depletion. Abnormalities in baroreceptor function are intrinsic to the pathophysiology of congestive heart failure and may subserve the vasoconstrictive and volume overloaded state that is responsible for patient morbidity.

Receptors located in the heart and lungs (cardiopulmonary baroreceptors) and great vessels (arterial baroreceptors) respond to changes in pressure and volume by altering the activity of the sympathetic and parasympathetic nervous systems, by regulating the hypophyseal secretion of arginine vasopressin, and by indirectly altering the activity of the renin-angiotensin-aldosterone system. The receptors located in both atria and ventricles respond to changes in pressure and volume by relying inhibitory neural activity to the central nervous system via the vagus nerve. Mechanoreceptors in the carotid sinus and aortic arch also respond to local wall stretch by discharging inhibitory signals to the central nervous system via the glossopharyngeal nerve and vagus nerve, respectively. Stretch produces an augmentation of parasympathetic activity and inhibits sympathetic outflow and renin and vasopressin release. By altering regional sympathetic tone and circulating vasoactive hormones, cardiopulmonary and arterial baroreceptors may play a vital role in modulating regional blood flow.

Blunted baroreceptor responses to high cardiac filling pressures or depressed cardiac function reduce afferent signals that normally inhibit sympathetic efferent activity, vasopressin release, and indirectly, renin secretion. The resulting increase in neurohumoral activity mediates the redistribution of blood flow that occurs in this disorder. Limb blood flow is usually reduced and may be responsible for exercise intolerance.

Decreased renal blood flow and altered intrarenal hemodynamics contribute to sodium retention. In addition, renal vasoconstriction and elevated circulating levels of angiotensin II and vasopressin may contribute to hyponatremia by influencing free water intake and excretion. Hence, baroreceptor dysfunction may be a principal mechanism that contributes to neurohumoral activation and subsequent alteration in vascular resistance and sodium and water balance in congestive heart failure.

2. Sympathetic Nervous System

Heart failure, particularly in the advanced stages, is characterized by increased plasma levels and reduced myocardial stores of plasma norepinephrine.^{25, 26, 27, 28} The sympathetic nervous system is activated in patients with congestive heart failure, as determined by intraneural recordings of peripheral nerve activity and by the measurement of circulating catecholamines.^{29, 30} Despite the marked increase in sympathetic nerve traffic to the ventricle, myocardial levels of norepinephrine are generally depleted in this disorder. This depletion may occur either because of a defect in catecholamine synthesis or because of enhanced release of norepinephrine from the failing heart (perhaps related to a defect in neurotransmitter binding). The degree of activation of the sympathetic nervous system varies greatly among affected patients, but the intensity of the neurohormonal reaction seems to be proportional to the severity of the hemodynamic abnormalities in this diseases. Such neurohormonal activation becomes particularly apparent when the left ventricular ejection fraction decreases to <40%. The nature of these abnormalities is not well understood,³¹ but they presumably represent an attempt to maintain circulatory homeostasis.³²

It is now generally accepted that beta adrenoceptors, rather than being static entities, are dynamically regulated by a wide variety of drugs, hormones and pathologic and physiologic conditions.^{33, 34} One important and clinically relevant consequence of receptor regulation is the phenomenon of "desensitization." This seems to be a general mechanism of cellular adaptation, to the extent that there is a diminished cellular response after long-term exposure to agonists. Chronic exposure of cardiac beta adrenoceptors to high concentrations of norepinephrine may result in desensitization and this may account for an impaired responsiveness to adrenoceptor stimulation.^{35, 36} Desensitization may occur either because of internalization of receptors, a rapid process occurring over several hours, or because of down-regulation, a longer process involving destruction of the receptor. Evidence from several groups³⁷ has shown that the total beta-receptor numbers are reduced in CHF. However, while beta 1 receptors are substantially decreased, beta 2 receptors remain mostly unaffected and it has been suggested that they may compensate for the loss of beta 1-adrenoceptor function and help to maintain contractility. The concept, however, that desensitization results only from beta receptor down-regulation has recently been challenged.^{38, 39} The response to various agents, such as isoproterenol, milrinone, amrinone and

theophyllines, was markedly depressed compared with the response to calcium. If desensitization occurs at the level of the beta receptor, it would be expected that the dose-response curve for isoproterenol alone would be reduced. Since the response to other drugs is also reduced, the defect has to be further down in the contractile pathway. There is much evidence to suggest that this abnormality lies in the sarcoplasmic reticulum, but the precise location of the defect is not clear.^{40, 41} A key factor may be the amount of cyclic adenosine monophosphate within the cell.⁴¹

Catecholamines are known to be toxic to the human myocardium⁴² and may contribute to serious ventricular arrhythmias,⁴² which are omnipresent in this patient population.⁴³ Based on these ideas some authors have suggested the use of low doses of beta-blockers in patients with advanced heart failure.⁴⁴ There is now a sense that excessive sympathetic drive may actually contribute to the pathogenesis of heart failure. These concepts, however, are not shared by everyone. Although recognizing that neurohormonal stimulation is a marked for the severity of heart failure, Cohn⁴⁵ believes that it does not necessarily play a primary pathogenetic role in the progression of the disease. Although vasoconstriction seems to be an important factor in this progression, the neurohormonal contribution to such systemic vasoconstriction may not be critical. The prevailing concept, however, is that it is important.

3. Renin-angiotensin-aldosterone system

It has long been known that plasma renin activity is increased in patients with heart failure.⁴⁶ Renin acts on renin substrate or angiotensinogen to produce angiotensin I, which is cleaved by converting enzyme to form angiotensin II. Mechanisms responsible for releasing renin from the kidney in heart failure include (1) beta 1-adrenoceptor stimulation in the kidney from enhanced sympathetic drive, (2) a perception by the kidney that there is a reduction in circulating volume/pressure (this is mediated by the baroreceptor stretch mechanism in renal vascular tissue), (3) a sensing by the macula densa of hyponatremic perfusate, and (4) diuretic use. Angiotensin II is a potent direct arteriolar constrictor and may facilitate further the release of norepinephrine from terminal sympathetic nerve endings.⁴⁷ This effect may account for at least one-half of the pressor response of angiotensin II.⁴⁸ Additionally, angiotensin II acts on the adrenal cortex to release aldosterone, a potent salt-and-water-retaining hormone. Aldosterone also has a potent kaliuretic effect, thereby contributing to hypokalemia.

Although the formation of angiotensin II might be expected to support systemic perfusion and glomerular filtration pressures, prolonged activation of this system seems to be accompanied by specific detrimental hemodynamic and biochemical consequences. Angiotensin is a potent systemic vasoconstrictor and potentiates the activity as well as the actions of other vasoconstrictor systems (for example, the sympathetic nervous system and vasopressin). Angiotensin also stimulates the release of aldosterone and thereby causes sodium and water retention. Acting in concert, these two primary

physiologic effects of angiotensin markedly increase loading condition in the failing heart and may accelerate progression of the underlying cardiac disorder.

Although the kidney is the likely source of most of the renin there is growing acknowledgement of the importance of the tissue renin-angiotensin system. Recently, a novel concept has emerged that challenges the traditional belief that the renin-angiotensin system is solely an endocrine system.⁴⁹ This concept proposes that endogenous renin-angiotensin systems are present in many local tissues and that these systems exert autocrine and paracrine influences on local tissue functions. The existence of local renin-angiotensin systems is supported by multiple lines of evidence deriving from the biochemical demonstrations of renin-like enzymatic activity, renin substrate, ACE, angiotensins, and angiotensin receptors in multiple tissues. Immunohistochemical and molecular biology techniques, have clearly demonstrated that both renin and angiotensinogen genes are expressed in the major organs that play important roles in cardiorenal homeostasis, i.e., kidney, adrenal, brain, heart, and blood vessels.

The implications of the possible effects of a local renin-angiotensin system are tremendous. Locally produced angiotensin may influence vascular function through paracrine or autocrine effects. For example, vascular angiotensin may effect the contractile state of the blood vessel. Smooth muscle cell derived angiotensin may induce vasoconstriction by activating its own angiotensin receptors and those on adjacent smooth muscle cells. Local angiotensin may enhance norepinephrine release from noradrenergic nerve endings in blood vessels. Endothelial-derived angiotensin may also exert a paracrine contractile influence on smooth muscle cells. In addition, this vasoactive peptide may influence endothelial prostacyclin biosynthesis. Implied actions of the vascular renin-angiotensin system include: (1) regulation of regional vascular tone and blood flow (2) pathogenesis of chronic hypertension, (3) determination of responses to pharmacologic inhibitors of the renin-angiotensin system (e.g., ACE inhibitor) (4) development of vascular hypertrophy, and (5) contributions to vascular responses to inflammation and injury.⁴⁹

Experimental evidence suggests several possible physiologic roles for the cardiac renin angiotensin system: (1) coronary vasoconstriction, (2) increased cardiac contractility, (3) stimulation of cardiac myocyte growth (hypertrophy), (4) influence on myocardial metabolism during ischemia and reperfusion injury, and (5) influence ventricular arrhythmias during ischemia and reperfusion injury. Based on these observations, Dzau has proposed a very interesting hypothesis⁵⁰ in which he proposes that the RAS consists of two compartments, one in the circulation and the other in local tissues. He believes that the principal function of the circulating renin-angiotensin system is to provide short-term cardiorenal homeostasis while the intrinsic tissue RAS influences the tonic control of vascular resistance and local tissue function (e.g., adrenal and kidney). To illustrate his point he has established an analogy between the renin-angiotensin system and the sympathetic nervous system. The tonic control of sympathetic function is provided by local

noradrenergic nerve activity. During the flight-or-flight response, additional support is provided by the acute release of catecholamines from the endocrine adrenal medulla. Similarly, the local renin-angiotensin system may have tonic influence on cardiac, renal, and vascular function. During cardiovascular decompensation, the endocrine renin-angiotensin system is activated for acute homeostasis. Another interesting point raised by Dzau is that ACE inhibitors may exert their principal action at local tissue sites. We will examine this subject further during the discussion of the treatment of congestive heart failure with ACE inhibitors.

4. Vasopressin

The antidiuretic hormone arginine-vasopressin (AVP) is an important and powerful endogenous vasoconstrictor that has been known for many years to increase during heart failure.⁵¹ Angiotensin II is known to increase AVP, but the precise stimuli that raise AVP levels during heart failure are not well defined. Small changes in the baseline vasopressin level do increase vascular resistance and lower cardiac output in patients with heart failure.⁵² AVP levels are frequently increased in parallel to a rise in plasma renin activity, in part because compromise end-organ perfusion and baroreceptor dysfunction is a common stimulus to both vasopressin and renin release and in part because angiotensin II may directly stimulate the hypophyseal production of vasopressin.⁵³ It is possible that the hyponatremia seen in patients with advanced heart failure may be related to the effect of AVP on a vasopressin 2 (V2) renal tubular receptor, causing a relative inability to excrete water normally.⁵⁴ There are no data, to date, that suggest that vasopressin exerts a direct deleterious effect on survival in this disorder.

5. Prostaglandins

To offset the vasoconstrictor/sodium-retentive forces activated in heart failure, nature unleashes a number of endogenous vasodilator natriuretic substances. Prostaglandin E2 (PGE2) metabolites and prostaglandin F-one-alpha are increased in hyponatremic patients with congestive heart failure.⁵⁵ PGE2, which is made in vascular smooth muscle, appears to be released in response to reduced tissue perfusion. Norepinephrine and angiotensin II also promote the release of PGE2. The actual importance of the prostanoids in heart failure is not clear. However, prostaglandins are manufactured, released, and act locally to subserve vasodilation in regional vascular beds. PGE2 may be particularly important in maintaining adequate renal function during reduced cardiac output. This fact is highlighted by the now well known fact that nonsteroidal anti-inflammatory agents can markedly impair renal function and even worsen pump function in patients with advanced heart failure and hyponatremia.⁵⁵ It is likely that enhanced PGE2 release is most important in patients with very low cardiac output and insufficient renal blood flow.

6. Atrial Natriuretic Factor

Mammalian atria contain secretory granules. In response to atrial distension, increased extracellular sodium or tachycardia, these granules release a peptide known as ANF or atrial natriuretic factor. Once in the circulation, ANF exerts a number of biologic effects that are mediated, at least in part, by cyclic guanosine monophosphate. Vasorelaxation of constricted vessels, natriuresis and fluid extravasation are among the observed effects of this new hormone. Additionally, ANF suppresses renin and aldosterone release and inhibits vasopressin action. Circulating levels of atrial natriuretic factor (ANF) are elevated in patients with congestive heart failure,⁵⁶ probably in response to the marked atrial distension that accompanies the elevation of right and left atrial pressures.¹² Plasma levels of ANF bear a direct relation to the hemodynamic and clinical severity of the underlying disease state. Many of the physiologic actions of ANF directly oppose the effects of the renin-angiotensin system, and thus, like the prostaglandins, atrial peptides may serve to counteract many of the detrimental circulatory and renal effect of endogenous vasoconstrictor hormones. Elucidation of the physiologic role of ANF in congestive heart failure awaits future studies.

7. Dopamine

Dopamine is a natural precursor of norepinephrine and can be secreted via exocytosis during sympathetic nerve stimulation. Patients with heart failure often have increased levels of plasma dopamine.⁵⁷ As with other vasodilator natriuretic substances, increased dopamine may be acting to offset excessive vasoconstrictor-sodium retentive forces found in these patients.

Determinants of Survival in Congestive Heart Failure

Patients with congestive heart failure have a poor long-term prognosis; the annual mortality rate in this disease varies from 10 to 50% depending on its clinical severity and mode of presentation.⁵⁸ Three patterns of death can usually be discerned: 1) sudden, unexpected death, occurring in approximately 40% of patients; 2) progressive, worsening heart failure occurring in about 40%; and 3) new cardiovascular or intercurrent events (such as myocardial infarction, pulmonary or arterial emboli or pneumonia), occurring in approximately 20% of patients.

A number of factors have been identified that appear to identify patients at high and low risk of death: 1) symptoms; 2) cardiac function; 3) exercise capacity; 4) ventricular arrhythmias; and 5) neurohormonal activity.

A. Symptoms

Patients with severe symptoms of heart failure (New York Heart Association functional class IV) have a 1 year mortality rate exceeding 50%, whereas those with milder symptoms have an annual mortality rate of only 10 to 20%. More importantly, patients who present with progressive symptoms have a much poorer prognosis than do those who are clinically stable,⁵⁹ perhaps because cardiac function is rapidly deteriorating in these patients

or because cardiovascular homeostasis can only be achieved at a price that is associated with high risk. Once symptoms are well established, the underlying cause does not appear to have prognostic importance.

B. Cardiac function

In the general population of cardiac patients, measures of ventricular systolic performance, particularly the ejection fraction, are powerful predictors of long-term outcome. In patients with chronic heart failure, however, the range of values for left ventricular function is relatively constricted (that is, most patients have a left ventricular ejection fraction <40%); consequently, indexes of cardiac performance have substantially less predictive power. Nonetheless, patients with the most compromised left ventricular function (as evidenced of an ejection fraction <20%, a stroke work index <30 g-m/m² or left ventricular function (as evidenced by an ejection fraction 20%, a stroke work index 30 g-m/m² or a left ventricular filling pressure >30mm Hg) have the most unfavorable long-term prognosis.⁵⁸ Some workers,^{60, 61} have suggested that indexes of right ventricular function also provide independent prognostic information, but this has not been the case in other studies.^{62, 63}

Severely impaired exercise is a powerful predictor of the long-term outcome of patients with chronic heart failure that is independent of the severity of cardiac dysfunction.⁶⁴ This observation is consistent with previous reports that exercise tolerance and ventricular function are not closely related^{64, 65} and it suggests that factors other than cardiac function must be important in determining the delivery of oxygen to and the utilization of oxygen by the peripheral organs, particularly by exercising muscles.⁶⁶ The variability in the peripheral adaptation to a decline in cardiac performance determines the clinical presentation of patients with chronic heart failure and may have important effects on prognosis. When objective measurements of symptomatic limitation, such as exercise tolerance, are used the demarcation between survivors and nonsurvivors is even more distinct. Individuals with maximum oxygen consumption (VO₂) of less than 10ml/min/kg had a 77% mortality at 1 year, compared with a 21% mortality in patients with a higher maximum VO₂.⁶⁷ It should be emphasized, however, that these data reflect the experience of referral centers that deal with the sickest patients and those with the most refractory disease. Symptoms and exercise capacity are less powerful predictors of mortality in subjects with mild symptoms.

E. Neurohormonal activation

We have just reviewed how neurohormonal systems are activated to various degrees in many patients with congestive heart failure. In general patients with high circulating levels of vasoactive neurohormones have more severe or more rapidly progressive heart failure, although this condition may not be reflected by hemodynamic measurements obtained at a single point in time. Such patients also usually require higher doses of diuretics, have a greater reduction in regional blood flow

and exhibit more frequent and complex ventricular arrhythmias than do patients with little evidence of neurohormonal activity.⁷⁰ Data published by Cohn suggested that an increased circulating plasma level of norepinephrine was the most important independent predictor of survival in patients with congestive heart failure.⁷¹ A more recent review of their data showed that the relationship between plasma norepinephrine and mortality is not linear and that levels above 600pg/ml are associated with the poorer prognosis.⁷² They also reported that the left ventricular ejection fraction and the maximal oxygen consumption during exercise were independent predictors of mortality. Hyponatremia has been recognized to be an indicator of increased circulating levels of neurohormones in patients with left ventricular dysfunction.^{73, 74} It is, therefore, not surprising that neurohormonal activation (as measured by plasma norepinephrine, plasma renin activity or serum sodium concentration) is a poor prognostic finding in patients with chronic heart failure.

Drug Therapy of Congestive Heart Failure

Dramatic changes in the management of patients with congestive heart failure have occurred in the last several years. The consistent clinical improvement obtained by the addition of vasodilators, specifically angiotensin converting enzyme (ACE) inhibitors, even in advanced stages of the syndrome and the recent demonstration of a benefit on survival, both for direct acting vasodilators¹ and ACE inhibitors,^{2, 3} has changed our traditional approach to its treatment. Diuretics remain the mainstay of therapy for CHF, regardless of other drug therapy that may be employed, although this concept has also been explored by Sutton.⁷⁵ Diuretics are not only useful in antagonizing the salt retention that follows a fall in renal blood flow, but they may be particularly useful in preventing the sodium and water retention that may follow the administration of direct-acting vasodilator drugs.

A. Inotropic agents

1. Digitalis

Digitalis is time-honored therapy for congestive heart failure. It produces a mild inotropic effect by inhibiting membrane sodium-potassium ATPase activity, which leads to enhanced calcium entry into the cell.⁷⁶ Its utility in patients with congestive heart failure complicated by rapid atrial fibrillation is well established, but its efficacy in patients in sinus rhythm has recently been questioned. In some studies the discontinuation of digitalis in patients receiving long term treatment with the drug failed to be accompanied by significant deleterious effects.⁷⁷ The lack of clinical deterioration after the withdrawal of digitalis was confirmed in another double-blind, placebo-controlled trial by Gheorghade et al.⁷⁸, who noted no significant changes in symptoms, left ventricular ejection fraction or exercise duration in patients with chronic heart failure in whom digitalis was withdrawn for 1 month. In another, recently completed study, Fleg⁷⁹ demonstrated no benefit from digitalis in exercise capacity in spite of some hemodynamic improvements. Some studies have found the benefit of digitalis

limited to patients with a dilated heart and a third heart sound.⁸⁰ Several other studies tend to support the contention that digitalis benefits in patients with congestive heart failure in sinus rhythm is for the most part limited to patients with the most advanced disease with the greatest left ventricular dilation, the lowest ejection fraction, and the most limited exercise capacity.^{80, 81, 82, 83} Some have suggested that digitalis therapy should be used primarily in patients with severe chronic heart failure who remain hemodynamically or clinically decompensated after optimal therapy with diuretics and vasodilators.⁸⁴ Further support to these ideas may be found in the report of the recently completed multicenter comparison of captopril and digoxin in mild to moderate heart failure.⁸⁵ In that study 300 patients, with mild to moderate symptoms, were randomly assigned to received placebo or digitalis after treatment with diuretics. Only patients treated with captopril showed a significant improvement in exercise tolerance and in functional capacity when compared to placebo, although the difference between captopril and digoxin-treated patients was not significant. The patients taking digitalis had a slight, but significant, increase in ejection fraction. A slight increase in the digoxin group, and a slight decrease in the captopril group in the frequency of ventricular ectopic beats was noted but the differences were not statistically significant. Two recently published reviews of the therapy of congestive heart failure have concluded that the benefits of digitalis in patients treated with diuretics had not been established.^{86, 87} Altogether these data suggest that, in the absence of atrial fibrillation, the use of digitalis in congestive heart failure should be limited to patients with well documented systolic dysfunction and cardiac dilation. A third heart sound appears to be a very convenient and easy way of confirming its need, or questioning its usefulness. Furthermore, discontinuation of digitalis seems warranted in patients without these findings.

2. Amrinone/milrinone

These drugs exert their inotropic effect by inhibiting the enzyme phosphodiesterase, which leads to increased levels of cyclic AMP, protein phosphorylation, and enhanced calcium entry into the cell. They also exert a potent vasodilator effect, for which they are often referred to as "inodilator drugs". The available data on long-term efficacy are consistent in showing little or no benefit.⁸⁸

3. B-agonist

This group include drugs with full B1 agonist activity such as dobutamine, those with partial B1 agonist effect such as xamoterol and prenalterol, and B2 agonist effect such as pirbuterol. The experience in clinical trials is limited. The oral form of prenalterol has been withdrawn from the market, and a trend toward a higher mortality among treated patients with ventricular arrhythmias led to the withdrawal of dobutamine. A large European trial of xamoterol showed a favorable trend in mortality.⁸⁸

B. Beta-adrenergic blockers

By blocking increased sympathetic activity and "up regulating" B-receptors, very small doses of B-blockers appear to produce symptomatic improvement in a subset of patients with congestive heart failure. Three small, randomized, controlled trials have assessed the efficacy of metoprolol in patients with dilated cardiomyopathy, and 1 trial evaluated acebutolol. The mortality data are very limited, so that no conclusions can be reached in this respect, symptomatic benefits have been reported by some.

C. Vasodilator drugs

1. Arterial vasodilators

a. Hydralazine. Hydralazine is a potent, direct acting vasodilator drug that causes relaxation of arteriolar resistance vessels, with little effect on the venous bed. In patients who have a normal left ventricular function, reflex activation of the sympathetic nervous system and renin-angiotensin system is a predictable consequence of therapy with this drug; such stimulatory actions are markedly attenuated in patients with heart failure. In such patients, hydralazine produces an increase in cardiac output and decrease in systemic vascular resistance, accompanied by little change in mean arterial pressure or heart rate.⁸⁹ Despite these apparent hemodynamic benefits, however, placebo-controlled studies have not been able to show that hydralazine produces a sustained increase in exercise tolerance in CHF patients during long-term therapy.⁹⁰ Furthermore, the doses required for effective hydralazine therapy have been quite variable, ranging from 200 to 800mg daily. Combined with isosorbide it has been shown to improve survival.

b. Minoxidil. This is a potent arteriolar vasodilator whose hemodynamic effects are quite similar to those of hydralazine.⁹¹ As in the case of hydralazine, minoxidil has not been shown to increase exercise tolerance in a placebo-controlled trial, and the potential for fluid retention of this drug does not make an attractive drug for the treatment of CHF.

c. Calcium-entry blockers. Nifedipine, verapamil, and diltiazem are direct-acting arteriolar dilators that reduce systemic vascular resistance. The increase in cardiac output produced by these drugs is less than with conventional arteriolar dilators.^{92, 93, 94} These agents exert additional direct negative inotropic effects, however, and thus they have a potential to directly depress cardiac function. Although the net clinical outcome depends on the balance between their ability to reduce afterload and their negative inotropism they do not represent a reasonable alternative to other vasodilators with similar or better hemodynamic profile and without the negative inotropic properties.

2. Venodilator drugs

a. Nitrates. The predominant hemodynamic effect of nitrate therapy is a reduction in right and left ventricular filling pressures. Although in the treatment of angina such hemodynamic effects may become attenuated, particularly during prolonged therapy, this appa-

rently has not translated into a significant problem in the treatment of congestive heart failure. Studies with oral nitrates have shown no acute change in exercise tolerance despite a notable reduction in ventricular filling pressures, however, during long-term treatment exercise tolerance has been shown to improve significantly in patients treated with isosorbide dinitrate.⁹⁵ The combination of isosorbide dinitrate and hydralazine has been shown to improve survival in patients with heart failure.

3. Vasodilators with mixed actions

a. Prazosin.

This drug is a quinazoline derivative that selectively blocks postsynaptic α -receptors. Prazosin, in general, does not appear to produce sustained benefit in terms of either improvement in clinical status or exercise tolerance. Attenuation of the systemic hemodynamic effects during prazosin therapy has been documented.⁹⁶ Likewise, no long term benefit from the use of Prazosin was demonstrated in the Veterans Administration cooperative study in congestive heart failure (V-HeFT).¹

b. Angiotensin-converting enzyme inhibitors

Oral angiotensin-converting enzyme inhibitors such as captopril and enalapril exert their hemodynamic effects primarily by decreasing the formation of angiotensin II, but as angiotensin converting enzyme is also involved in the degradation of some vasodilator kinins, they may also promote the synthesis of endogenous kinins and prostaglandins, which may contribute significantly to the hemodynamic effects of these drugs.^{97, 98} These drugs produce a modest increase in cardiac output accompanied by a notable reduction in ventricular filling pressures; mean arterial pressure falls without an accompanying tachycardia. The reduction in blood pressure may be quite marked and although sometimes well tolerated, represents the most important potentially deleterious hemodynamic effect of therapy. Placebo-controlled studies with captopril and enalapril have shown that they produce an amelioration of symptoms and an increase in exercise tolerance in patients with moderate-to-severe congestive heart failure, in addition to prolonging their life.⁹⁹

Differentiation of Inhibitors of the Renin-Angiotensin System

Inhibitors of the renin-angiotensin system may differ from one another based on (1) pharmacology (2) their differential effects on circulating and tissue renin-angiotensin system (RAS), and (3) other nonrenin-angiotensin-mediated effects.

A. Differences in pharmacologic characteristics

Three chemical classes of angiotensin-converting enzyme inhibitors have been introduced into clinical use, the sulfhydryl-containing (SH-) inhibitors such as captopril and its analogs, carboxyalkyldipeptides such as enalapril and its analogs, and phosphorus-containing inhibitors such as fosinopril and the phosphonate SQ 29,552. Within each of the three groups of inhibitors significant differences in molecular weight and polarities can be observed. These differences have a significant

influence in the routes of elimination and tissue distribution of these inhibitors. Tissue distribution and intrinsic potency will determine the magnitude of angiotensin-converting enzyme inhibitor at the tissue level, which could play a critical role in the clinical utilization of these inhibitors. Other physicochemical properties may determine differences in the distribution and penetration of ACE inhibitors. For example, it is conceivable that a lipophilic ACE inhibitor penetrates and accumulates in the central nervous system more readily and exerts a greater effect on the brain renin-angiotensin system than a hydrophilic compound. Similarly, other physicochemical properties may influence the distribution of these drugs in other tissues. For instance enalapril is a prodrug that must be converted to the active drug, enalaprilat, for its action. Indeed, captopril and enalapril appear to differ with respect to relative concentration and duration of action in certain tissues.

There is another aspect in which there is a marked difference between the different classes. The carboxy-alkyldipeptide angiotensin converting enzyme inhibitors, like enalapril and its analogs, and the phosphorus-containing inhibitors, like fosinopril and SQ 29,852, undergo a very limited metabolism, except for the conversion to the active drug in those cases where an ester prodrug is utilized. However, the sulfhydryl-containing angiotensin converting enzyme inhibitors undergo a rather complex scheme of reversible modifications through interactions with themselves or other endogenous sulfhydryl-containing compounds to form symmetrical or mixed disulfides.¹⁰⁰ All these disulfides can regenerate captopril and constitute, therefore, depot forms of the drug. Also, captopril can be converted into disulfides through the interaction with free radicals, and in this process it may serve as a free radical scavenger. Since the disulfide can be converted back into free captopril, the system can function as a recyclable antioxidant. This effect may be of importance for the cardioprotective action of captopril¹⁰¹ as was shown by Westlin in dogs submitted to a period of 15 min of ischemia. In this preparation, pretreatment with sulfhydryl-containing ACE inhibitors only, resulted in a 40% to 60% return to active shortening within 60 min of reperfusion. Both types of ACE inhibitors, however, reduced the incidence of ventricular fibrillation produced by reperfusion, suggesting that the capacity to inhibit ACE confers these drugs with their antifibrillatory actions while the capacity to act as free-radicals scavengers is pertinent to the sulfhydryl group. Another possible benefit of these actions is in the generation of SH-compounds that may be beneficial in reducing nitrate tolerance.

B. Differential effect on circulating vs. tissue RAS

The drug's chemical structure and physicochemical property may play an important role in determining the differences in the penetration and distribution of different ACE inhibitors in the heart, blood vessels, and other tissues. In addition, certain ACE inhibitors may have unique effects attributable to a unique property of the specific drug e.g., the presence of the sulfhydryl group.

Some of these differences have been alluded to already.

The distribution of ACE inhibition in tissues of the spontaneously hypertensive rat (SHR) after the oral administration of captopril and enalapril has been examined by Cohen and Kurz.¹⁰² Enalapril showed an overall delayed onset of tissue ACE inhibition as compared with captopril. Captopril produce a more rapid and marked inhibition of brain ACE whereas enalapril had a delayed and weaker inhibition. Both inhibitors produced a prolonged duration (2 to 5 days) of inhibition of ACE activities in lung, aorta and kidney after the discontinuation of the drugs, while serum, heart, and brain ACE activities rapidly returned to normal (within 24 hr). Inhibition appeared greater in the blood vessels (aorta) than in other tissues with both drugs, but enalapril produced greater inhibition of renal ACE than did captopril. A similar comparative study was performed with enalapril and ramipril by Unger et al.¹⁰³ Ramipril produced a significant greater inhibition of lung ACE. Otherwise both inhibitors induced prolonged aortic and kidney ACE inhibition. Additional differences between the action of ACE inhibitors were demonstrated by Antonaccio and McGill.¹⁰⁴ In the pithed SHR, captopril significantly inhibited the pressor responses to sympathetic nerve stimulation and norepinephrine, while enalapril had no effect. It was suggested that only captopril interfered with sympathetic responses. This might have resulted from the differential penetration and distribution of this drug in the blood vessel wall. Indeed, in the intact SHR as well as in the isolated perfused kidney, captopril blocked vascular responses to norepinephrine infusion into the renal artery more effectively than did enalapril.¹⁰⁵

It must be stressed here that the clinical significance of these differences is unclear and remains to be elucidated.

C. Effects mediated by nonrenin-angiotensin mechanisms

The pharmacology of angiotensin converting enzyme inhibitors is dictated by the interaction of three very important humoral systems: the renin-angiotensin, the kallikrein-kinin, and the eicosanoid (arachidonic acid cascade) systems. It is clear that in their interactions with the first two systems, the three chemical classes of inhibitors that have been described behave similarly, with differences that are mostly a reflection of their intrinsic potency, and pharmacokinetic properties. These differences can be of importance since the renin-angiotensin and the kallikrein-kinin systems may serve important autoregulatory functions. Although the immediate depressor response to ACE inhibitors in humans correlates with the initial plasma renin activity, the long-term response appears to bear little relationship to pretreatment plasma hormonal levels.¹⁰⁶ Clearly, ACE inhibitors can lower blood pressure in many hypertensive patients whose plasma renin levels are normal or even low. This observation is supported further by animal studies that have demonstrated that the administration of ACE inhibitors lowers the blood pressure in various hypertensive animal preparations in which plasma renin activities are not elevated.¹⁰⁷

Several postulates have been proposed to explain the

nonrenin-mediated antihypertensive effect of these antagonists. Since ACE also degrades bradykinin, it has been suggested that an accumulation of tissue bradykinin resulting from the inhibition of this enzyme might be responsible for the additional vasodilating effect.¹⁰⁸ Another hypothesis proposed that inhibition of the renin-angiotensin system resulted in a reduction in sympathetic nervous activity through a reduction in catecholamine release at noradrenergic nerve endings.¹⁰⁹ Alterations in baroreceptor reflex activity has been suggested as another possible mechanism. Current evidence also suggests a prostaglandin-mediated effect of captopril. Plasma prostaglandin E2 metabolite levels have been observed to increase after the administration of captopril. The mechanism by which captopril stimulates prostaglandin E2 biosynthesis is not clear. Zusman¹¹⁰ demonstrated that captopril stimulated prostaglandin E2 biosynthesis in cultured renomedullary interstitial cells in vitro. This effect appears to be somewhat unique to captopril since enalapril failed to stimulate prostaglandin release from these cells. This observation is supported by the clinical data of Given et al,¹¹¹ who failed to observe an increase in plasma prostaglandin E2 metabolites after administration of enalapril.

In summary there is growing evidence that the effects of ACE inhibitors depend on a combination of factors dependent, to a large extent, in their specific pharmacologic properties and in their relative effect on the circulating and on the tissue RAS. The clinical significance of these differences remain to be elucidated.

Efficacy of Vasodilators Drugs in the Treatment of CHF

The main goals in the treatment of CHF are: 1) improve cardiac performance, 2) improve symptoms, and 3) improve survival.

A. Improve cardiac performance

Cardiac performance can be improved by inotropic agents, by decreasing preload with venodilators, or by

decreasing afterload by arterial dilators. The latter two objectives can be accomplished by vasodilators with mixed venous and arterial dilating capacity. We have already discussed the value and controversies regarding the use of inotropic agents.

B. Improve symptoms

Direct acting arterial vasodilators, when used alone, have not been shown to improve exercise tolerance in patients with CHF. Venodilators, on the contrary, do improve symptoms during long-term therapy,⁹⁵ and the combination of isosorbide and hydralazine improves survival as will be discussed below.

There is extensive evidence of the clinical benefits of ACE inhibitors in the treatment of patients with severe heart failure, both from the point of view of symptoms and, most recently, of survival.^{96, 2, 3} The evidence in patients with milder forms of the syndrome is not abundant. Moreover, although ACE inhibitors exert potent hemodynamic changes in patients with a highly activated renin-angiotensin system, the evidence for a favorable profile in patients with less severe heart failure is scarce. We recently completed a study of the effects of intravenous captopril in a small number of patients with congestive heart failure who were in NYHA functional class II to III. All patients had a radionuclide determined ejection fraction of less than 40%. After a period of stabilization of diuretics and digitalis doses (no vasodilator) the patients had a right sided cardiac catheter (Swan-Ganz) inserted the day prior to the study. The morning of the study hemodynamic stability was determined and then captopril was infused in increasing doses of 2, 4, 6, and 8 mg at intervals of 10 min (Table 1). Hemodynamic measurements were repeated after each intravenous dose. As shown in the table, in spite of only slightly abnormal hemodynamics at baseline, captopril produced a prompt and significant hemodynamic improvement in SVR, CI, and PCW. Although this data lacks correlation with the simultaneously determined degree of RAS activation, it

Table 1. EFFECTS OF INTRAVENOUS CAPTOPRIL IN HEART FAILURE

<u>Time (min)</u>	<u>BL</u>	<u>10</u>	<u>20</u>	<u>30</u>	<u>45</u>
<u>Dose (mg)</u>	0	2	4	6	8
<u>CI (L/m/m²)</u>	2.6	2.9	3.0*	2.9*	2.8
<u>PCW (mm Hg)</u>	14	12	11	11	11 [†]
<u>RVS (dyne sec⁻¹)</u>	1496	1329*	1221*	1221*	1305*

N=9 for all values * p < .05 † p < .01

BL=Baseline; CL=Cardiac index; SVR=Systemic vascular resistance; PCW=Pulmonary capillary wedge Gallardo I, Hernández E, et al. Bol Asoc Med PR 1987; 79:268

Table 2. LONG-TERM EFFECTS OF ENALAPRIL IN HEART FAILURE

<u>N</u>	<u>AGE</u>	<u>EF</u>		<u>Exercise Tolerance (secs.)</u>			<u>NYHA Class</u>	
		<u>BL</u>	<u>48wk</u>	<u>BL</u>	<u>48wk</u>	<u>Δ</u>	<u>BL</u>	<u>48wk</u>
6	61.5	27%	28%*	403	560	+167*	2.8	1.8†
* p = NS		† p < .05						

does suggest that even in milder stages of congestive heart failure captopril produces a significant hemodynamic benefit. A recently published study of the treatment of mild to moderate heart failure with captopril¹¹² is further evidence of this contention.

Enalapril, a carboxyalkyldipeptide, is another ACE inhibitor that has been shown to improve survival in patients with severe CHF.² As part of a multicenter study on the use of enalapril in patients with CHF we evaluated 9 patients with NYHA functional class II to III treated with this drug in doses between 2.5mg and 20 mg bid. The data of the 6 patients who reached at least 48 weeks of follow up is presented in Table 2. Although the changes in exercise tolerance in this cohort were not statistically significant, there was an improvement in the patients' well being as evidenced by an improvement in the NYHA functional classification. The combined data also showed a significant benefit in terms of exercise tolerance.¹¹³

The overall experience suggest that besides isosorbide dinitrate, ACE inhibitors, are the only vasodilators to have been shown to improve the symptoms of congestive heart failure.

C. Improve survival

Three recently published studies have documented the beneficial effects of vasodilators in improving survival in patients with chronic congestive heart failure.

1. The Veterans Administration Cooperative Study,¹ randomized 642 patients to receive placebo, prazosin (20 mg/d), or a combination of hydralazine (300 mg/d) and isosorbide dinitrate (160 mg/d). There was a decrease in mortality in the combination group of about 28% at an average of 2.3 years which was of borderline statistical significance. The benefit of the combination was seen regardless of age, degree of LV dysfunction, severity of CHF, or etiology of the syndrome. No benefit in survival was provided by the use of prazosin.

Critique: There was a high incidence of side effects of the combination of isosorbide and hydralazine. A total of 32% of the patients discontinued either drug or both, and only 55% of the patients were taking full doses of both drugs 6 months after randomization.

2. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)² randomized 253 patients,

functional class IV, to receive placebo or enalapril (2.5 mg to 40mg daily) in addition to conventional treatment of CHF with digitalis, diuretics, and in about one third of the patients other vasodilators (except ACE inhibitors). Enalapril reduced mortality by approximately 40% at 6 months after randomization and by 27% by the end of the study.

Critique: This study included only patients with severe symptoms (NYHA class IV) and of an advanced age (mean age=71 years). There was a relatively high incidence of hypotension with the higher doses of enalapril.

3. The Captopril Multicenter Research Group randomized 105, NYHA functional class II to III, patients to placebo or captopril up to 100 mg tid. During the 90 days double-blind portion of this study, 21% (11 of 52) of placebo-assigned patients died compared with 4% (2 of 53) of captopril-assigned patients (p<0.01).

Critique: This was a smaller study than the previous two and included a shorter period of observation.

Summary

The data herein presented provides persuasive evidence that in addition to diuretics, and probably digitalis (since all studies have included subjects taking this drug) patients with congestive heart failure should also be placed on a vasodilator regimen to slow the progression of the syndrome and to reduce its mortality. Firm recommendations for the choice of drug and the selection of patients likely to benefit from this treatment must await the results of further studies. At present, ACE inhibitors are preferred because they are usually better tolerated than conventional vasodilators and are clinically more effective. In regard to the question of when to begin vasodilator it is noteworthy that neurohormonal activation may occur early in the course of the disease, even before symptoms appear. If so, perhaps vasodilators should be initiated even in the asymptomatic stage of left ventricular dysfunction to prevent the progressive dilatation and deterioration that lead to clinical heart failure. The just published study of the efficacy of captopril in preventing the progression of left ventricular dilatation in patients with a recent anterior, transmural myocardial infarction supports this view.¹¹⁴ Further, ongoing studies, will help place these issues in their proper perspective.

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CME REVIEW QUIZ

Select the best answer:

1. The following abnormalities of the neurohormonal systems have been described in patients with CHF, except:
 - a. blunted baroreceptor responses.
 - b. increased levels of circulating catecholamines.
 - c. intense parasympathetic activity.
 - d. "down-regulation" of cardiac beta-receptors.
 - e. depletion of cardiac catecholamines stores.
2. The benefits of digitalis in patients with congestive heart failure has recently been challenged. Two clinical findings useful in identifying patients likely to benefit from digitalis are:
 - a. severe dyspnea on exertion and chest pain at rest.
 - b. orthopnea and severe left ventricular hypertrophy.
 - c. an increased cardio-thoracic ratio and fatigue.
 - d. cardiomegaly and the presence of a third heart sound.
 - e. distended neck veins and severe fatigue.
3. Among the systems activated in congestive heart failure, the following is thought to exert a beneficial hemodynamic effect:
 - a. atrial natriuretic factor (ANF).
 - b. tissue renin-angiotensin system.
 - c. down-regulation of cardiac B-receptors
 - d. increased levels of circulating vasodilator catecholamines.
 - e. increased parasympathetic tone.
4. The following type of drugs have been demonstrated to both improve symptoms of patients with congestive heart failure and improve their long-term survival:
 - a. inotropic agents.
 - b. direct arterial vasodilators.
 - c. angiotensin-converting enzyme inhibitors.
 - d. beta-receptor blockers.
 - e. calcium channel blockers.

Answer True or False to the following statements:

5. One of the cellular mechanisms that have been proposed to contribute to the progression of congestive heart failure is a decrease in high energy phosphate stores in spite of an increase in mitochondrial number density.
6. The blunted baroreceptors response seen in patients with congestive heart failure help explain, in part, the decreased levels of circulating catecholamines seen in some of these patients.
7. Despite the lack of a strong correlation between the left ventricular function and the exercise tolerance they have been found to be good predictive indexes of the long term prognosis in patients with congestive heart failure.
8. Some of the most important differences that have been described between the angiotensin-converting enzyme inhibitors may be explained on the basis of the presence of a sulfhydryl group in some of them.
9. The ability of some of the angiotensin-converting enzyme inhibitors of stimulating the production of Thromboxane helps explain their capacity to lower the blood pressure in hypertensive patients with low renin levels.
10. Of patients with congestive heart failure symptoms, the least likely to benefit from digitalis therapy are those with predominantly diastolic dysfunction of the left ventricle.



EDUCACION MEDICA CONTINUADA

La Asociación Médica de Puerto Rico (AMPR) es una institución acreditada para ofrecer Educación Médica Continuada (EMC). La AMPR ha determinado que este ejercicio académico reúne los criterios para 1 hora-crédito de EMC categoría I para la Asociación Médica Americana y para la oficina de Reglamentación y Certificación de Profesionales de la Salud. Al final del año se enviará un Certificado de 6 créditos a quienes hayan cumplido los requisitos. Para obtener crédito favor de seguir las instrucciones que se detallan a continuación.

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Estado Actual de la Insulinoterapia y Otras Formas de Tratamiento en las Psicosis*

José D. Jiménez, MD**

Vamos a considerar primeramente la insulinoterapia que es la adquisición más valiosa para la Psiquiatría durante la última década. El tratamiento recomendado por Sakel consiste en administración progresiva de dosis de insulina empezando con 5 ó 10 unidades y aumentando 10 unidades diariamente hasta obtener un estado comatoso. La inyección se practicará de 6:30 a 7:00 de la mañana y se permitirá que el paciente permanezca en cama sin tomar desayuno durante 4 ó 5 horas. Durante las primeras inyecciones los pacientes experimentan en fases progresivas, primero sudoración abundante, sensación de hambre, palpitaciones y finalmente se llega al estado de crisis convulsiva o se cae en un estado comatoso. Una vez pasadas las 4 horas se le dará a tomar 200 cc de solución glucosada, después de lo cual el paciente descansará un rato y una vez desaparecidos los síntomas de hipoglicemia tomará su almuerzo y después puede hacer la vida corriente. Se recomienda dejar descansar un día a la semana y administrar un tratamiento no menor de 60 shocks comatosos o convulsivos según sea el caso. Se han reportado en la literatura extranjera numerosos casos desgraciados de muerte con estos tratamientos y para evitar ésto, Sakel recomienda interrumpir el estado comatoso o la hipoglicemia tan pronto el pulso decaiga o sea más lento de 50 por minuto. Sakel recomienda el uso de la sonda esofágica para pasar una solución glucosada al estómago y en el curso de 15 minutos todos los síntomas molestos de la hipoglicemia desaparecen. Sólo como medida de emergencia extrema recomienda el uso de glucosa por vía intravenosa, así como el uso de tonicardíacos, adrenalina, etc. Nuestra experiencia con esta forma de tratamiento ha sido la siguiente: empezamos a administrarle al enfermo 10 unidades de insulina y nunca pasamos de 100 unidades. Si no se ha llegado a producir el estado comatoso empezamos a disminuir la dosis en 10 unidades diariamente y es nuestra experiencia que enfermos que anteriormente no tenían síntomas de hipoglicemia con dosis de 100 unidades, luego con dosis de 60 ó 40 unidades se producía el shock deseado. En algunos enfermos administramos la insulina

en idéntica forma, pero evitamos en lo posible que se produzca el estado convulsivo, tipo epileptoide y, solamente llegamos al estado de excitación con contracturas musculares, lo cual permitimos se prolongue durante un máximo de una hora. Cuando los enfermos están en estado de shock hipoglicémico y no pueden ingerir la solución glucosada, entonces usamos la inyección intravenosa de 20 cc de glucosa al 50%. Preferimos de esta manera devolver al enfermo al estado de consciencia en el término de un minuto. El uso de la sonda esofágica para administrar la glucosa nos parece algo tardía en sus efectos. Felizmente aunque en algunos casos nos han sobrevenido complicaciones alarmantes, no hemos tenido que lamentar casos fatales con esta modalidad terapéutica. Esta forma de tratamiento ha sido empleada preferentemente en casos de demencia precoz reciente, en sus cuatro tipos (paranoide, catatónico, simple y hebefrénico). Es nuestra experiencia que en las formas paranoide, o catatónica recientes, el éxito es muy halagador y generalmente devolvemos al ambiente del hogar completamente restablecidos a estos enfermos después de dos meses de hospitalización. En la demencia precoz simple y hebefrenia, esta terapia al igual que cualquier otra forma de terapéutica, es mucho menos efectiva y sólo un 30% de los casos recientes mejoran satisfactoriamente con esta forma de terapia. Enfermos de tipo paranoide o catatónico de más de un año de duración, reaccionan de manera menos favorable y es nuestra experiencia que en pacientes con más de 5 años de enfermedad la mejoría obtenida ha sido muy poco duradera, podríamos más bien decir que la terapéutica ha sido completamente ineficaz. También hemos ensayado la insulinoterapia en otras formas de psicosis, tal como en la psicosis maniaco depresiva. En la psicosis maniaco depresiva, tipo depresiva, hemos obtenido resultados halagadores en un 50% de los casos, pero en las formas maníacas, con gran excitación psicomotora, generalmente hemos tenido que suspender el tratamiento debido a shocks inesperados y hemos desistido por completo de administrar esta forma de terapia en este tipo de psicosis. En la melancolía involucional, que como se sabe es un cuadro de la menopausa en que predominan las reacciones afectivas, tipo depresivo, ideas de ruina, autoacusaciones, etc., el tratamiento ha sido poco satisfactorio. Nosotros hemos desistido de aventurarnos con esta forma de tratamiento en pacientes de más de 45 años,

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no importa la forma de psicosis que padezcan. Es nuestra experiencia que en pacientes tuberculosos que aparentemente estaban arrestados, se le ha reactivado su condición pulmonar con esta clase de tratamiento. Enfermos con intermitencias cardíacas o lesiones cardíacas de otra forma también han empeorado en sus lesiones orgánicas al administrarle la insulinoterapia. En algunas formas de histeria, hemos obtenido muy buenas reacciones con este tratamiento, pero en casos severos de hemiplegia histerica o crisis epileptiforme, tipo histericoso, no han respondido favorablemente. También hemos ensayado el shock insulínico en los estados neuróticos sin éxito aparente.

Narcosis Prolongada

Otra forma de tratamiento muy eficaz que actualmente está siendo estudiada en Norte América, es el de la narcosis prolongada. Hace cuatro años que nosotros a iniciativa propia y sin guiarnos por otros autores, estamos usando el amital sódico como droga favorita en el tratamiento por la narcosis prolongada. Enfermos maníacos con una incontinencia verborreica, gran excitación psicomotora, fuga de ideas, actitud expansiva, etc., son sometidos a esta forma de tratamiento lo más pronto posible después de su ingreso. Nosotros empezamos administrando 20 cgm. de amital sódico cada 3 horas desde las 6:00 de la mañana hasta las 9:00 de la noche. Durante la noche no se le da drogas a los pacientes. La dosis se va administrando "*in crescendo*", ésto es, luego una cápsula cada 2 1/2 horas; al tercer día cada dos horas, cuarto día dos cápsulas cada tres horas; quinto día dos cápsulas cada dos horas y media; sexto día dos cápsulas cada dos horas. Esta es la dosis máxima que hemos llegado a administrar a pacientes para obtener una completa sedación. Durante el tratamiento le damos alimentación cada vez que se le da la droga. Una vez que se ha obtenido la sedación completa se mantiene el tratamiento durante no menos de 10 días. Si es posible y si se ha obtenido una sedación completa, la medicación se va disminuyendo hasta que se obtenga la sedación deseada con la menor cantidad de droga. Nosotros tenemos conocimiento de otros autores que han usado hasta 15 gramos de amital sódico al día por vía oral. Nuestro máximo es de tres gramos. En casos en que llegamos al máximo por nosotros recomendado y no se obtiene la sedación, entonces continuamos esta misma dosis aunque el paciente continúe excitado e interrumpimos el tratamiento al final del décimo día de la dosis máxima. Casi todos los enfermos tienen una reacción febril que puede llegar a 38°C y décimas, mientras están sometidos a dosis altas de amital sódico. La fiebre desaparece tan pronto se suspende el tratamiento. Es nuestra experiencia que pacientes que se han mantenido excitados a pesar del tratamiento, al segundo o tercer día de interrumpida la narcosis, vuelven a un estado de casi completa normalidad. Igual pasa con los otros casos en que se obtiene la sedación deseada durante el tratamiento. En algunas ocasiones en que el enfermo, pasados unos días recae nuevamente en un período de excitación, nosotros volvemos nuevamente a repetirle este tratamiento aunque por un período más corto.

Recientemente la narcosis prolongada se ha usado para despertar a los pacientes catatónicos, que como ustedes saben son completamente apáticos, en completo mutismo y permanecen largas horas en actitud estatuesca. Se pensaría que en enfermos aparentemente deprimidos el amital sódico estaría contraindicado, sin embargo, autores norteamericanos alegan que una narcosis prolongada rompe el ciclo de autismo y se logra establecer un "rapport" con el médico, hasta que finalmente el paciente vuelve a la normalidad. Nosotros no hemos tenido experiencias en este sentido, en dementes precoces, pero sí en estados depresivos de la psicosis maníaca depresiva que algunas veces simulan una catatonía.

Alcanfor Cardiazol

Otros tratamientos usados actualmente y que nosotros hemos ensayado repetidas veces son las inyecciones de aceite alcanforado a dosis progresivas, y las inyecciones intravenosas de cardiazol (metrazol). Nyiro y Jablonsky hicieron la feliz observación de la incompatibilidad entre la epilepsia y la demencia precoz y que en enfermos en que coexistían estas enfermedades, los ataques iban desapareciendo a medida que progresaban los síntomas de demencia precoz. Meduna en Budapest concibió la idea de contrarrestar el avance de la demencia precoz por medio de ataques epileptiformes.

Se alega por muchos autores que empezando con una dosis inicial de 8 cc dos veces al día de aceite alcanforado al 25% y aumentando de 4 a 6cc diarios, se puede llegar hasta una dosis de 56cc o sea 14gr., dosis que no debe sobrepasarse. En el curso del tratamiento cuando se ha llegado a la dosis necesaria en que se produce la convulsión, la misma dosis se repite dos o tres días más tarde y así sucesivamente se continúa administrando las inyecciones durante dos o tres meses hasta tener el tratamiento deseado. Las convulsiones tienen lugar de 15 minutos a tres horas después de la inyección. Usando el metrazol o sea el cardiazol, se empieza con una dosis intravenosa de 5cc de solución al 10%, la cual se administrará en días alternos y se aumenta 1cc hasta que se obtiene la dosis convulsiva, después de lo cual esta misma dosis se administra de 20 a 30 veces. El máximo de dosis ha sido fijado en 16cc. Cuando se usa la inyección de metrazol se obtiene una sola severa crisis convulsiva que tiene lugar casi instantáneamente. No se administrarán barbitúricos a menos que persista un ligero estado de intranquilidad psicomotora después de la crisis convulsiva. Esta forma de terapéutica se recomienda como muy eficaz en las formas estuporosas. Es necesario en esta forma de tratamiento establecer un umbral de mayor irritabilidad y sin peligro para el enfermo. Esto se obtiene administrando alcalinos, así como una gran cantidad de líquido, pues sabido es que la alcalinización es tetanizante y convulsivante por sí misma. Se recomienda darle de uno a dos gramos de bicarbonato de sodio tres veces al día y tomar un mínimo de dos litros de líquido en las 24 horas. Muchos investigadores de la esquizofrenia son de opinión de que la enfermedad va acompañada por alteraciones del metabolismo y de cambios químicos patológicos. Los cambios orgánicos que van produciéndose lentamente tienden a un retardamiento o regresión del organismo hacia estados primitivos. Las crisis

convulsivas producen una irritación y estimulación que contrarresta el bloqueo metabólico que se había establecido durante la psicosis. Los cambios químicos y metabólicos producidos por el status epiléptico facilita el funcionamiento de las vías normales de la ideación que hasta entonces habían estado bloqueadas.

Nosotros hemos usado el tratamiento de inyecciones de aceite alcanforado habiendo obtenido crisis convulsiva con 40 y 50 cc de aceite alcanforado. La convulsión ha sobrevenido de manera inesperada y ha sido de muy corta duración y los enfermos han caído subitamente al suelo sin que haya dado tiempo para prestársele ayuda y evitar puedan lesionarse. Comoquiera que el número de pacientes nuestros es limitado y en pacientes recientes hemos usado con muy buen éxito el shock insulínico, hemos tenido que ensayar esta forma de tratamiento en pacientes crónicos que cooperan muy mal.

Muy a pesar nuestro la repetición de las dosis convulsivantes administradas dos o tres días más tarde, no producían la convulsión como era de esperarse y muchas veces ni aún administrándole dosis mucho mayores. La inyecciones de cardiazol por vía intravenosa han sido ensayadas y en realidad producen una convulsión, pero el precio de dicha droga en el mercado locales prohibitivo y la dosis mínima nos cuesta más de \$1.00, lo cual a dosis mayores hace excesivamente costoso esta forma de tratamiento.

En conclusión nuestra experiencia con el tratamiento de aceite alcanforado es la siguiente: Pacientes crónicos, ésto es, de más de tres años de enfermedad, mejoran rápidamente después de la convulsión, pero como no nos es posible obtener el estado convulsivo repetidamente, el tratamiento resulta poco práctico. Nuestros enfermos crónicos han rehusado tomar sustancias alcalinas, rehusan tomar excesos de líquido y sólo bajo medidas restrictivas se consigue mantenerlos en cama. Un enfermo que está caminando y expuesto a una crisis convulsiva, corre gran riesgo y se expone a recibir heridas al caer al suelo. Las inyecciones intravenosas de cardiazol, es cierto, que producen una convulsión inmediata, pero lo violento de las contracturas nos han hecho temer por la seguridad del enfermo.

La Lobulotomía o Leucotomía

La lobulotomía frontal empleada primeramente por Egas Moniz en Portugal ha sido recomendada como tratamiento quirúrgico ideal en ciertas formas de psicosis con gran ansiedad, así como también en las neurosis obsesivas. Las experiencias de varios cirujanos, entre ellos Fulton y otros, habían llamado la atención sobre los cambios afectivos observados en lesiones traumáticas del lóbulo frontal. La atenuación de los síntomas de ansiedad, después de traumatismos hizo pensar a Egas Moniz en la conveniencia de practicar la lobulotomía prefrontal en las neurosis obsesivas rebeldes a toda forma de tratamiento. Freeman en Washington, ha operado

algunos casos de este tipo de enfermos y alega que han mejorado considerablemente a los pocos días de operados, sin que se haya notado indicios de deterioro intelectual. Una paciente nuestra que fue operada por el Dr. Freeman; posteriormente recibió un tratamiento por psicoanálisis, está actualmente tomando un curso de matemáticas avanzadas en la Universidad de Columbia. Nosotros no hemos intentado esta forma de tratamiento, cuya técnica es sencilla y aparentemente de muy poco riesgo, pero creyendo que la operación en sí destruye zonas nobles que pueden causar daños irreparables, no nos hemos atrevido a aventurarnos en esta forma de terapéutica quirúrgica de la psiconeurosis.

La técnica de la lobulotomía prefrontal recomendada por Moniz es la siguiente: Se le da al paciente en su habitación media hora antes de la operación, de 80 a 85 mg. por kg. de peso de alcohol tribrometilico. Se hace una incisión en cada lóbulo frontal 3 cm. lateral a la línea media que pasa 3 cm. por delante de la oreja. Se hacen las dos incisiones laterales de 3 cm. de longitud y paralelas a la línea media. Se marcará en el periosteo el sitio de la incisión a fin de no perder el sitio de localización al hacer tracción sobre el cuero cabelludo. Se hace la perforación ósea y luego se hará la incisión en la dura, pia-aracnoide de la manera más cuidadosa a fin de evitar hemorragias molestas. Se introduce el leucotomo o cánula de lobulotomía en dirección antero-medial hasta una profundidad de 4 cm. de la superficie de la corteza. Se presiona el estilete para formar un arco en la porción distal del instrumento y luego rotando la cánula para formar un círculo completo que corta una esfera de masa encefálica de aproximadamente 1 cm. de diámetro. Se le quita la presión al estilete para que desaparezca el arco y luego se retira el estilete un poco hacia arriba y se hace otra esfera a una profundidad de 3 cm. Igualmente se hace otra esfera al nivel de 2 cms. Se saca por completo el estilete y se reintroduce en dirección anterolateral en el mismo lóbulo prefrontal donde se cortan tres esferas de masa encefálica a los niveles de $4\frac{1}{2}$, $3\frac{1}{2}$ o $2\frac{1}{2}$ cms. Una vez producidas estas seis esferas en cada uno de los lóbulos frontales se pueden visualizar las lesiones producidas, inyectando por cánula cerebral una solución de dióxido de torio la cual es opaca a los rayos-x.

Freeman recomienda no ser muy conservador en la extirpación pues los resultados no serían efectivos. No hay temor a hemorragias, pues esta masa cerebral no es vascularizada en su interior y los vasos meningeos han sido evitados al separar las meninges.

La teoría de este tratamiento es que cortando un gran número de filamentos nerviosos conductores de reacciones afectivas, se destruyen de esta manera la excitación de estados angustiosos. No puede negarse que el paciente siempre pierde algo de su destreza, iniciativa y algo de su personalidad, pero no debe perderse de vista que este es un tratamiento de emergencia para cuando todas las otras formas de terapia han fracasado.

El Dr. José D. Jiménez: Pionero de la Psiquiatría Biológica en Puerto Rico

Miguel A. González-Manrique, MD*

Durante los años veinte de este siglo nuestro *amamentarium* psiquiátrico era muy limitado y escaso. Para el tratamiento de la demencia precoz, hoy psicosis y desórdenes esquizofrénicos, así como para los desórdenes afectivos, solo contabamos con un centro institucional, el Asilo de Beneficencia. Como medidas terapéuticas, solo la hidroterapia y la camisa de fuerza. Para las psicosis, hoy desórdenes de ansiedad, existía el psicoanálisis el cual para su desarrollo recibió la exclusiva atención de la psiquiatría durante varias décadas.

En la década de los treinta y respondiendo a la necesidad de “tratar” más que de cuidar al paciente mental severamente enfermo, un puñado de psiquiatras puertorriqueños adiestrados en los Estados Unidos inician la práctica de la psiquiatría privada en Puerto Rico. Con cautela, comienzan a utilizar las técnicas terapéuticas más recientes publicadas en la literatura médica de la época. Estas se encontraban en una etapa temprana de investigación por sus iniciadores a quienes yo les llamo los “experimentadores empíricos de la psiquiatría.” Ellos buscaban una cura física para las psicosis, dada su demostrada resistencia al psicoanálisis.

Julius Wagner Ritter Von Jauregg (Austria) recibió el Premio Nobel de Medicina en 1927 al minimizar el deterioro de la demencia sifilítica inoculando a sus pacientes con malaria, provocándoles hipertermias que en ocasiones precipitaban estados convulsivos. Manfred Sakel inducía 5 a 6 horas de coma hipoglucémico, pasando por convulsiones, para tratar la narcomanía. Observó cambios favorables en el apetito y el sueño así como la disminución de la ansiedad. Luego usó la misma técnica con pacientes agudamente psicóticos reportando un 70% de remisión sintomática. Ladislav Von Meduna convencido de los beneficios del estado convulsivo sobre la esquizofrenia provocó convulsiones con alcanfor y luego con metrazol endovenoso. En Estados Unidos, Bleckwenn (1929) usó el amital sódico endovenoso para tranquilizar y dormir a pacientes psicóticos así como para activar y movilizar a los catatónicos. Weir Mitchell siguiendo la misma línea popularizó su famosa “cura del sueño”. Egas Moniz, otro Premio Nobel de Medicina (1949) comenzó la práctica de la psicocirugía en el Hospital St. Elizabeth en Washington, D.C. Disecando partes del lóbulo frontal y sus conexiones con el tálamo lograba atenuar conductas agresivas, destructivas y obsesivo-compulsivas en pacientes mentales crónicos. Como secuela permanente quedaba una indiferencia en

las respuestas emotivas normales ante estímulos externos como por ejemplo: coraje, tristeza o alegría. También prevalecía una falta de iniciativa y motivación generalizada.

Es en el mismo Hospital St. Elizabeth donde el Dr. José D. Jiménez (1900 - 1984) completó su adiestramiento como neuropsiquiatra. En su biblioteca personal encontré múltiples trabajos y apuntes propios sobre neuroanatomía comparada y experimentos en neurofisiología animal, pruebas de su convencimiento de que el desarrollo de la psiquiatría descansaba en el conocimiento de sus bases biológicas. Al leer la bibliografía del trabajo que nos compete, reconocemos que estaba al día con las últimas publicaciones internacionales. No solo fue uno de los pioneros que duplicó las técnicas en Puerto Rico sino que también las modificó y hoy, al evaluarlas retrospectivamente nos indican su buen juicio clínico dado el alto riesgo de las mismas. Como ejemplo de lo último, fue su cautela con las dosis de insulina, barbitúricos y cardiazol así como la inmediata utilización de la glucosa endovenosa en lugar de la vía oral o por sonda gástrica para contrarrestar de inmediato las consecuencias irreversibles del coma insulínico.

Gracias a los resultados obtenidos internacionalmente al experimental con estas técnicas, pudo concluirse que el efecto terapéutico común a ellas fue el producido por el estado convulsivo. El doctor Jiménez nos ofrece una versión simple y generalizada de su mecanismo de acción, la cual no difiere mucho de la que tenemos hoy en día: mayor cantidad de neurotransmisores (nor-epinefrina) en los espacios sinápticos del diencefalo y el sistema límbico. Fueron estas conclusiones las que llevaron a Cerletti y Bini (Italia) a introducir en el 1940 la terapia electroconvulsiva la cual substituyó completamente a la insulina y al cardiazol, convirtiéndose en la terapia principal para la esquizofrenia y la depresión hasta la llegada de los neurolepticos y los antidepresivos en el 1955. En Puerto Rico en el año 1950 se aplicaron 1,056 choques eléctricos en el Hospital Estatal de Psiquiatría, aumentando a 35,368 durante el año fiscal 1953-54

Es interesante señalar las observaciones que hace el doctor Jiménez basado en su propia experiencia sobre los resultados positivos obtenidos con la insulina y el cardiazol en pacientes agudos y sub-agudos paranoides, catatónicos y deprimidos bipolares. Todavía en la actualidad la terapia electroconvulsiva se indica para estos pacientes a excepción de los paranoides. La pregunta que surge de inmediato es si existe una base etiopatogénica (¿genética?) común a estas entidades. La respuesta aún descansa en futuras investigaciones.

Solo la narcoterapia y la psicocirugía han sobrevivido hasta nuestros días. La primera ya no se utiliza para

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tranquilizar, sedar o dormir al paciente pues hoy disponemos de los neurolépticos, las benzodiazepinas y el carbonato de litio. Actualmente los barbitúricos de acción corta usados en forma endovenosa facilitan "entrevistas" reveladoras de información reprimida o reactivan las reacciones emotivas ("abreaction") que acompañan a un severo trauma psicológico ("post-traumatic stress disorder") promoviendo la modificación o el agotamiento de conductas relacionadas al mismo. Ya no se usa el pentotal sódico para movilizar a pacientes catatónicos, pues la mayoría revierte a la catatónica pasado el efecto medicamentoso o pueden precipitarse reacciones de excitación destructivas durante el mismo.

La psicocirugía nunca fue muy popular en Puerto Rico y no tengo conocimiento fuese realizada a nivel privado. En el año fiscal 1949-50 se realizaron 13 lobotomías prefrontales en el Hospital Estatal de Psiquiatría. Dos pacientes fallecieron por complicaciones quirúrgicas y otro desarrolló trastorno de tipo convulsivo. Precisamente estas fueron las complicaciones que detuvieron el progreso de esta técnica a nivel internacional. En los Estados Unidos de Norteamérica esta técnica todavía tiene seguidores y se practica en pacientes agresivos criminales, en desórdenes obsesivos-compulsivos crónicos severos resistentes a otras modalidades terapéuticas y también en depresiones severas, crónicas intratables. La

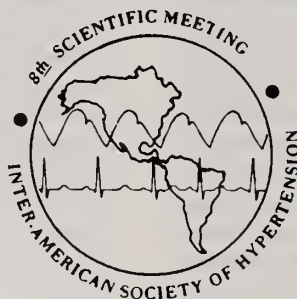
indiferencia afectiva irreversible no ha podido ser minimizada, por lo que esta técnica siempre despierta conflictos de carácter ético-médico. Con la introducción reciente de nuevos fármacos, como la clomipramina, en el tratamiento de esta condición es probable que esta técnica pase a la historia.

El trabajo del doctor Jiménez nos ubica en la perspectiva histórica, permitiéndonos reconocer el rápido avance de nuestra especialidad en los últimos cincuenta años, así como nuestras posibilidades de desarrollo en el campo de la psiquiatría biológica que comenzó en los años treinta y hoy se encuentra en pleno apogeo.

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VIII SCIENTIFIC MEETING INTER-AMERICAN SOCIETY OF HYPERTENSION



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GENERAL INFORMATION

DATE: May 13 - 17, 1989

SITE: Caribe Hilton International Hotel,
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SATELLITE SYMPOSIA

Satellite symposia are also planned.

May 13 (Sat). - 17 (Wed.), 1989
SAN JUAN, PUERTO RICO

IMPORTANT DATES

Deadline for receipt of abstracts November 21, 1988
Notification of Abstract acceptance January 30, 1989
Deadline for pre-registration March 15, 1989

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Dilemas de la Práctica de la Medicina para el Siglo XXI

Ética y Ciencia: El Gran Dilema del Siglo XXI

Anibal Marín, MD*

Este año académico, similar al año pasado, el Departamento de Medicina de Familia del Recinto de Ciencias Médicas de la Universidad de Puerto Rico se ha propuesto llevar a cabo una serie de conferencias alrededor de un tema central de actualidad y de interés general para toda la comunidad académica del Recinto. El año pasado el tema central giraba alrededor de la práctica de la medicina para el año 2000 y se presentaron varios conferenciantes que entre otros temas hablaron sobre la medicina y los envejecientes, la mujer como proveedora de servicios médicos, el equipo de salud y alternativas en la prestación de servicios médicos.

Este año se presentarán conferenciantes que expondrán sus puntos de vista en áreas donde existen conflictos de índole ético-médico y que al presente estos se debaten por la comunidad médica como por ejemplo: el trasplante de órganos, la confidencialidad del paciente, la eutanasia, relación médico-paciente, y otros.

Esta serie de conferencias se publicará en el Boletín mensualmente, ya que creemos será de gran interés para nuestros lectores. Esperamos que por la naturaleza de los temas a presentarse, éstos provoquen reacción en nuestros lectores y escriban al editor con comentarios y otros puntos de vista.

Esta primera conferencia pretende identificar e ilustrar algunos principios éticos que se pueden aplicar en la toma de decisiones de dilemas o conflictos de índole ético-médico. Estos principios a su vez formarán el marco de referencia a utilizarse en los próximos temas y nos brindarán dirección en las presentaciones a seguir.

Por lo menos existen seis principios éticos generales que son fundamentales en la práctica de la medicina.

1. Primero, no hacer daño ("*primum non nocere*")
2. Preservar o mantener la vida
3. Aliviar el sufrimiento
4. Respeto a la autonomía del paciente
5. Concepto de justicia, distribución justa o imparcial de los recursos médicos
6. Honradez y claridad en la divulgación de información al paciente.

"*Primum non nocere*"

Este principio es tal vez uno de los axiomas más importantes del Juramento de Hipócrates y uno que ha dirigido la conducta del médico a través de los años. Sin embargo, todos reconocemos situaciones donde este principio se rompe como por ejemplo el caso de un embarazo causado por un ultraje en el cual la mujer decide no llevar a término su embarazo y el médico tiene que decidir si hacerle daño a la madre o al feto. Basándonos en este principio ético, ¿cuál sería la selección correcta? Esta situación en particular ha sido analizada y discutida en diferentes foros, y finalmente se ha decidido por la Iglesia y por las leyes que regulan la práctica de la medicina, que la madre está protegida y tiene derecho a exigir a que se le termine su embarazo terapéuticamente. De la misma forma, el médico tiene todo su derecho a rehusar llevar a cabo el procedimiento, si este conflige con sus creencias religiosas o convicciones morales y él o ella también están protegidos legalmente.

"*Primum non nocere*" - "primero no hacer daño" también se pueda interpretar como "el bien que se hace a otro"; es decir, beneficencia. Beneficencia significa caudal o bondad hacia otras personas; es decir benevoloso, que a su vez implica una acción voluntaria de la persona que es benevoloso. Sin embargo beneficencia en el contexto del axioma de Hipócrates se entiende que es obligatorio; es decir, el médico tiene que ser benevolente. Esta conducta benevolente del médico se complementa con su responsabilidad de maximizar los beneficios que le puede brindar al paciente y minimizar los daños o detrimentos que le pueda ocasionar.

Preservar o Mantener la Vida

Sobre este principio se habla mucho hoy en día. Todos hemos oído innumerables ponencias sobre la calidad de vida y las controversias existentes si se debe o no prolongar la vida por medios artificiales en los casos de coma irreversible o de enfermedad terminal. En muchos hospitales las siglas DNR ("*do not resuscitate*") se están utilizando en los expedientes médicos de pacientes con estas condiciones y éste representa una decisión y acción médica totalmente opuesta a este principio ético. Estas decisiones 30 ó 40 años atrás se hacían mucho más fáciles pues no teníamos todos los adelantos de la tecnología moderna para prolongar la vida que ahora disponemos.

Si reflexionamos sobre otro principio ético, el de "aliviar el sufrimiento", nos daremos cuenta que éste en muchas situaciones está en conflicto con el principio de "preservar o mantener la vida". Todos reconocemos situaciones donde al paciente se le mantiene "vivo" por medio de intervenciones que le causan dolor y sufrimiento, no solamente a él, sin también a su familia. Ante estas situaciones, muchas veces nos preguntamos para qué y por qué mantener una vida que dejó de tener cualidades humanas, a cambio de tanto dolor y sufrimiento.

Respeto a la Autonomía del Paciente

El respeto a la autonomía del paciente es un principio ético que realmente incorpora dos convicciones— uno es el que reconoce al paciente como un ser autónomo, independiente, que se gobierna por las leyes que a sí mismo se dicta; la otra convicción reconoce que aquellos individuos con autonomía disminuida merecen protección.

Una persona autónoma es un individuo capaz de deliberar sobre sus metas personales y actuar en la dirección de estas metas. Respetar la autonomía de una persona significa tener consideración a sus opiniones y preferencias y no obstruir sus acciones a menos que éstas serán perjudiciales a otras personas. No obstante, no todo ser humano es capaz de hacer sus propias decisiones. Esta capacidad se va adquiriendo según el individuo va madurando. Algunas personas pueden estar incapacitadas en parte o en su totalidad por enfermedad, incapacidad mental o por circunstancias que restringen severamente su libertad y a estos hay que protegerlos.

Conflicto con este principio de respecto a la autonomía del paciente lo vemos en los casos donde el paciente rehúsa tratamiento (ej.: Testigos de Jehova). La popularidad de los "living will" y según éstos se implementan ocasionara más conflictos en esta área de autonomía.

Concepto de Justicia

Tal vez la forma más apropiada de definir el concepto de justicia es reconociendo cuando ocurre injusticia; es decir, cuando el beneficio al cual una persona tiene derecho es negado sin justificación o cuando a esa persona se le castiga indebidamente. Otra forma de visualizar el concepto de justicia es el reconocer que todos los seres humanos se deben de tratar con igualdad. Sin embargo, sabemos que hay ocasiones en que se justifica que nos apartemos de este principio; como es el caso en que se le otorgue preferencia a los niños o personas incapacitadas. Por lo tanto es necesario identificar los parámetros a utilizarse en la distribución de beneficios. Los conocedores en esta materia han formulado unos parámetros para llevar a cabo la distribución y éstos se basan en: 1) que a cada persona se le dará una porción igual, 2) que a cada persona se le otorgará una porción de acuerdo a su necesidad, 3) que cada persona recibirá una porción a base de su esfuerzo demostrado, 4) distribución individual de acuerdo a su contribución a la sociedad, 5) distribución de acuerdo a su mérito.

Este concepto de justicia en muchos instantes se ha olvidado, principalmente al llevar a cabo investigación. Ejemplo de ésta ocurrió durante el siglo 19 y al principio

del siglo 20 cuando gran parte de la investigación en humanos se llevaba a cabo en pacientes de instituciones públicas. Sin embargo, los beneficios obtenidos de estos estudios solamente llegaban a pacientes en instituciones privadas. El ejemplo más dramático tal vez se la explotación de los prisioneros en los campos de concentración de la Alemania Nazi y a los cuales se le practicaron procedimientos que hoy reconocemos como atrocidades. En los años 40 en los Estados Unidos se llevó a cabo un estudio (Tuskegee Study) en el cual un grupo de hombres negros de comunidades rurales diagnosticados con sífilis no fueron tratados a propósito, para observarse el curso de la enfermedad sin tratamiento aún cuando luego se consiguió un tratamiento efectivo y accesible.

Todos estos ejemplos nos señalan la importancia de este principio ético de justicia, principalmente cuando se practica investigación en humanos. Hay que examinar bien a fondo si los sujetos a utilizarse son seleccionados simplemente por pertenecer a ciertas clases (recipientes de bienestar público, grupos minoritarios, residentes de instituciones penales) que los hacen fácilmente disponibles y manipulables o porque realmente presentan las características o problemas a estudiarse.

Honradez y Claridad en Divulgación de Información al Paciente.

Este principio ético es uno que con gran frecuencia sale a colación en los casos de impericia médica y por lo tanto es uno al cual el médico tiene que prestar mucha atención. Es responsabilidad del médico explicarle al paciente el procedimiento a practicarse o tratamiento a administrarse y brindarle la oportunidad al paciente, siempre y cuando éste tenga la capacidad mental para entenderlo, para seleccionar si lo acepta o no lo acepta. La forma de consentimiento inteligente o autorización ("informed consent") debe de contener como mínimo lo siguiente:

1. La naturaleza del procedimiento a practicarse o el tratamiento a llevarse a cabo, explicado en detalle y en unos términos que el paciente pueda entender.
2. El propósito del tratamiento o intervención.
3. Los riesgos envueltos.
4. Los resultados o beneficios que se esperan.
5. Otras alternativas que se pueden considerar, aunque estas no estén disponibles en su propia localidad.
6. Oportunidad para hacer preguntas.

Todos reconocemos situaciones donde el paciente no está en condiciones para dar su consentimiento propiamente. En esas circunstancias hay que identificar el familiar más cercano o la persona que se hace responsable de tomar las decisiones para el paciente y obtener el consentimiento de ellos.

Estos principios éticos generales aquí presentados muy rara vez se ven por sí solos en la práctica de la medicina; al contrario, en la mayoría de los casos con que nos enfrentamos en la medicina, estos principios se relacionan entre sí en el manejo de pacientes. En ocasiones para poder cumplir con algunos tenemos que obviar otros y viceversa. Todo caso tiene que individualizarse, ya que

cada uno conlleva sus propias circunstancias y peculiaridades y éstos hace la toma de decisiones mucho más difícil.

Este proceso de tomar decisiones hoy en día todavía se hace más difícil aún, pues tenemos a la mano adelantos científicos con los cuales no contábamos hace 15 ó 20 años, y que nos permiten llevar a cabo otras alternativas en el manejo del paciente. Si a todo esto le añadimos ciertos factores socioeconómicos y políticos característicos de nuestra sociedad moderna, como lo son el consumismo, el movimiento feminista, los derechos civiles y la heterogeneidad moral de nuestra propia sociedad, la práctica de la medicina se convierte ardua y laboriosa... pero nadie a dicho que practicar medicina es fácil.

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Fe de Errata

Por error involuntario se publicó en la sección de nuevos socios, en la edición de noviembre, Vol. 80, No. 11, al Doctor Ubaldo Bocanegra Acevedo como Médico Generalista, cuando debe leer Psiquiatra.

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Case Presentation

The Syndrome of Cerebral Infarction Following Herpes Zoster Ophthalmicus

Juan L. Joy, MD*
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Jesús R. Vélez-Borrás, MD**

Abstract: Delayed contralateral hemiparesis following herpes zoster (HZ) ophthalmicus is an unusual but distinct clinical entity, presumably caused by HZ-induced arteritis with subsequent cerebral infarction. We report a case showing typical clinical and angiographic findings.

Delayed contralateral hemiparesis after herpes zoster (HZ) ophthalmicus is an uncommon but well-defined clinical entity.¹⁻⁴ The time interval from infection to infarction varies from a few days to 6 months, with an average of about 8 weeks.^{1, 2} The pathogenesis is believed to be HZ-induced arteritis with subsequent cerebral infarction. Frequently, the histological changes are those of granulomatous angiitis of the nervous system.^{5, 6} We report a case showing the typical clinical and angiographic features.

Case Report

A 26-year-old male developed left HZ ophthalmicus followed in 3 months by an acute right hemiparesis and confusion. On admission he was drowsy, afebrile and without nuchal rigidity. Postherpetic scars were evident around his left eye and forehead. Neurologic examination showed a dense right hemiparesis with central facial weakness.

The CT demonstrated a large left hemispheric infarct involving most of the middle cerebral artery territory. Additionally, there were small deep infarcts in the left caudate nucleus and internal capsule. The cerebrospinal fluid (CSF) was clear and colorless with an opening pressure of 160 mmH₂O, protein 68 mg%, glucose 54 mg% (serum 85 mg%), 56 mononuclear cells/mm³, and 9 erythrocytes/mm³. Angiography revealed "beading" and complete occlusion of the left middle cerebral artery (Figure 1); there was also aneurysmatic dilatation

of the ipsilateral anterior cerebral artery's A₁ segment (Figure 1), consistent with arteritis.³

After treatment with acyclovir 300 mg I.V. every 8 hrs for 10 days his deficits partially resolved. At the time of discharge he had a mild residual right hemiparesis and dysphasia.

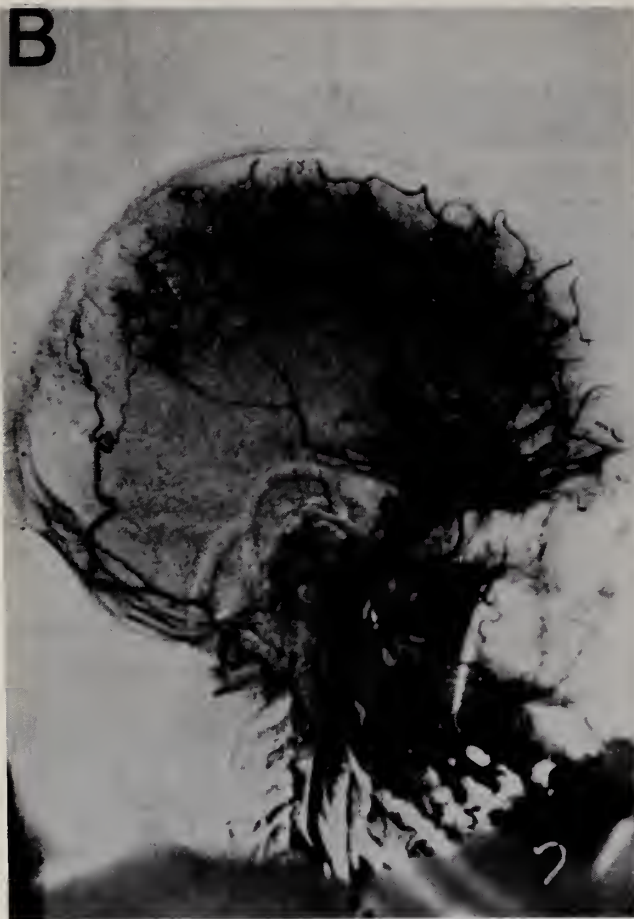


Figure 1. Left carotid angiogram showing complete occlusion (bold arrow) and irregular configuration (arrows) of the M₁ portion of the middle cerebral artery. Aneurysmatic dilatation of the A₁ segment of the anterior cerebral artery is also evident (curved arrow). On the lateral view (next page) there is absence of filling of the middle cerebral artery branches. Antero-posterior (A) and lateral (B) views.

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Discussion

The mechanism of HZ-associated angiitis is incompletely understood. Vasculitis might be a consequence of viral invasion of vessels since viral particles have been identified within the vessel wall.^{5, 7} The virus could reach the vessels by spreading along the intracranial branches of the trigeminal nerve.³ Although involvement of the homolateral arteries is most frequent,³ in several cases, bilateral angiographic abnormalities^{1, 4} or bihemispheric infarcts^{2, 7} occurred. Additionally, some individuals with cerebral HZ angiitis have had truncal rather than ophthalmic zoster.^{2, 6} In one case, contralateral infarction followed HZ oticus.⁸ It is apparent that other mechanisms are operating. In such patients either hematogenous or contiguous dissemination through CSF pathways must be invoked.

Even though ipsilateral infarction after HZ ophthalmicus is the most commonly described event, the syndrome comprises a broader clinical spectrum.

Resumen: La hemiparesis contralateral después de herpes zoster oftálmico es una entidad poco usual pero bien reconocida. Se cree que es causada por arteritis mediada por el virus, produciendo eventualmente infarto cerebral. Presentamos un caso el cual ilustra las características angiográficas típicas de esta condición.

por
Reporta
clínicas y a

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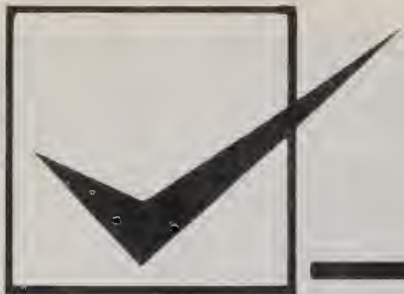
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SPECIAL ARTICLES

Anesthetic Considerations for Patients with Ischemic Heart Disease

The primary considerations for proper anesthetic technique in the dental office are the same whether or not the patient has cardiac disease. They include the scope of the procedure, the patient's cardiovascular status, the training of the person administering the anesthesia, and the psychological profile of the patient. Each day, patients with ischemic heart disease receive anesthetics for both cardiac and non-cardiac surgery with little morbidity or mortality. An adequate history of the patient's cardiac disease and proper selection of anesthetic technique are mandatory for safety of the procedure. Essential factors are a knowledge of the patient's disease process as provided by the individual's physician, and adequate monitoring of cardiac status and other vital signs. Sometimes when the cardiac status is in question, dental procedures are best performed in a hospital setting.

Review of Cardiac Physiology

The most frequent causes of cardiac disease in *adults* can be divided into two categories: valvular (obstructive or regurgitant) and ischemic coronary artery disease. Inadequate management of the stress of surgery can have detrimental effects on patients with either type of heart disease. This discussion is directed to ischemic heart disease.

Normal Oxygen Supply and Demand of the Heart

Normally, the oxygen supply and demand of the heart is balanced so that the myocardium has an adequate oxygen supply. In patients who have coronary artery obstruction, the supply of oxygen to the heart is fixed, while the oxygen demand varies with exercise and other forms of stress. Since the heart normally extracts most of the oxygen available from arterial blood, a major mechanism for increasing oxygen supply in the face of increased demand is an increase in coronary blood flow.

This compensation is limited when there is a fixed obstruction of the coronary arteries.

The oxygen demand of the heart is related to blood pressure, heart rate, left ventricular filling pressure and contractile state of the myocardium. Increases in any or all of these variables will increase the oxygen demand. In individuals with limited coronary blood flow the supply cannot be adequately increased (except by coronary artery revascularization surgery or balloon dilatation angioplasty); in these patients efforts should be made to limit the demand.

The Rate Pressure Product

The calculation of the rate pressure product (RPP) represents a clinically useful indication of the oxygen demand of the heart. The number is obtained by multiplying the systolic blood pressure by the heart rate. The RPP at a blood pressure of 120/80 and a pulse of 80 is 9600. Angina and insufficient coronary blood flow rarely occur at a RPP less than 12,000. Studies have shown that a patient who has angina pectoris will reproducibly develop angina and ECG changes of ischemia at a level of RPP specific for each patient (usually 12,000 or above). The combination of high blood pressure and low heart rate appears less detrimental than a low blood pressure and a high heart rate. It should be noted that the RPP is a measure that correlates with myocardial oxygen demand, not only external work. The RPP can be raised to levels necessary to cause cardiac ischemia even at rest for reasons such as anxiety, interoperative pain, or an intravascularly injected vasoconstrictor agent.

Electrocardiographic Changes

Myocardial ischemia leads to a change in the repolarization process of the ventricle, which is manifested by depression of the electrocardiogram in the segment between the QRS and the T (commonly referred to as ST segment). These changes are seen as often as 90 percent of the time in the V₅ chest lead in adults, less frequently in standard limb leads. For example, an increase in blood pressure can lead to myocardial ischemia and ST depression, and return of the blood pressure level to

normal can cause the ST segment to return to normal. Heavily premedicated patients may have hypertension and myocardial ischemia without complaining of chest pain.

History Taking in the Patient with Heart Disease

All patients over 40 years of age should be asked about the signs and symptoms of ischemic heart disease. However, it should be remembered that some persons with genetic susceptibility have the onset of coronary artery disease at a much younger age. Despite a classic history, angina can easily be misdiagnosed in younger patients.

Exertional Chest Pain

All individuals should be specifically questioned about chest or arm pain associated with physical exercise. The discomfort associated with coronary artery insufficiency is variable, ranging from severe pain in the left arm to a slight burning in the jaw (which can be mistaken for dental pain). A progressive increase in the severity of chest pain, a decrease in the amount of exercise necessary to elicit the chest pain, or a lack of relief of pain by rest or nitroglycerin tablets is an indication to postpone an intended dental or surgical procedure and to obtain evaluation by the patient's physician.

History of Myocardial Infarction

A history of myocardial infarction does not necessarily mean that the patient is at increased risk for a dental or surgical procedure. The period of time since the myocardial infarction is relevant; there is an increased risk of reinfarction within 6 weeks of a prior event. Within 3 months of a myocardial infarction there is approximately a 25% instance of reinfarction. Between 4 and 6 months after infarction, the reinfarction rate is 16%; after 6 months the incidence is the same as age-matched controls. The symptoms that occurred at the time of the initial myocardial infarction are also important in determining the relative incidence of later problems. Therefore, it is useful for the dentist in consultation with the patient's physician to be aware of these symptoms and make appropriate decisions regarding the proposed dental procedure.

History of Prior Coronary Artery Bypass Grafting Procedure

Based upon studies of nondental surgical procedures, it appears that prior myocardial revascularization without subsequent angina diminishes the incidence of cardiac events. Two different investigations showed that patients with prior coronary artery bypass grafting had no myocardial infarctions or cardiac-related deaths during subsequent noncardiac operations.^{1, 2} Whether these data apply to dental surgical procedures, however, has not been specifically studied.

History of Artificial Cardiac Pacemaker

Myocardial infarction frequently leads to a lack of normal generation and conduction of electrical activity

of the heart, resulting in the absence of a cardiac contraction. A pacemaker may be required. At last estimate, over 200,000 persons in this country had permanently implanted pacemakers, which are designed to function in either of two modes, depending on whether spontaneous activity is present (but erratic) or completely absent. In the fixed mode, pacing is carried out at a preset rate. In the demand mode, the pacemaker fires when spontaneous activity is absent and is inhibited (turned off) by spontaneous cardiac activity. Unfortunately, electrical activity other than from the heart can inhibit the pacemaker, causing asystole. The most frequent cause is the use of electrocautery; however, other electrical equipment, such as an electrical dental chair, has been shown to inhibit the pacemaker.³ Therefore, it is important to be aware of the type of pacemaker before dental treatment is initiated. The pulse should be palpated in these patients during the use of electrical equipment to make certain that inhibition has not occurred. If it is apparent that electrical activity is inhibiting the pacemaker, the electrical device should be turned off, and the pacemaker should begin to function normally.

Cardiac Medications of Interest

Digoxin

This drug is used to treat congestive heart failure or arrhythmias. Digoxin has a very low therapeutic-toxicity ratio, and toxicity is fairly frequent. Nausea, vomiting, and visual disturbances are frequent signs of toxicity. Arrhythmias may also indicate toxicity. These symptoms should be evaluated by the patient's physician in collaboration with the dental practitioner. Arrhythmias may be exacerbated by stress.

Antiarrhythmic Agents

Numerous drugs are used to suppress ventricular beats secondary to previous myocardial infarction. The patient should be able to tell the dentist if his arrhythmias are under control and what medication he is receiving. Poor control of arrhythmias is an indication to postpone an elective dental or surgical procedure until the patient can be evaluated by the physician.

Propranolol hydrochloride

Propranolol is a beta-adrenergic blocker used to decrease the anginal symptoms of patients with coronary artery disease. The effect is accomplished by decreasing both the resting heart rate and by modifying the heart rate response to stress. A resting heart rate of 50 to 60 beats per minute is not uncommon in these patients. The average dose is 160-320 mg per day in divided doses⁴ although higher doses have been reported.⁵ There is extreme variation in the bioavailability of the drug due to extensive first-pass metabolism by the liver.⁶ Studies in anesthetized patients have shown that propranolol does not blunt the increase in heart rate or blood pressure that occurs in response to anesthetic manipulations such as tracheal intubation or surgical stimulation.⁷ The patients on propranolol therapy had significantly lower resting heart rates, however, and their heart rates remained

below that of the untreated group throughout the study. The maximum RPP is presumed to be below that necessary to cause myocardial ischemia. Topical anesthesia and other maneuvers are often used to minimize the systemic cardiovascular response to these stressful stimuli.

It has been suggested that propranolol can be given to dental patients to relieve the cardiovascular consequences of anxiety, especially tachycardia. Studies reported in the psychiatric and dental literature indicate that a certain segment of the population is hypersensitive to the catecholamine responses of stress. This cycle of anxiety with catecholamine release, perception of the response, and further anxiety can apparently be reduced with a very low dose of propranolol. It should be pointed out that this does not represent beta-blockage adequate to protect the patient with ischemic heart disease from the stresses of surgery. Unless the dentist is familiar with the use of this drug, it should be used only in consultation with the physician.

Nitrates

The prototype of this drug group is sublingual nitroglycerin. Long-acting nitrates are also available. These agents function by several mechanisms, including direct action on the coronary arteries and systemic vasodilation with a decrease in blood pressure. Nitrates will stop an anginal attack in progress or increase the amount of exercise performed before angina occurs. Topical nitroglycerin preparations are also available. One type is the nitroglycerin "patch" which allows gradual absorption over 24 hours. There is also a lingual aerosol spray. Another currently used preparation is nitroglycerin-based paste. This preparation is applied to the skin of the forearm, back, or chest. By direct action the drug causes a decrease in blood pressure and a slight increase in heart rate. It is rapid in onset and lasts for approximately three hours. It has been shown to significantly increase the amount of cardiac work tolerated before the onset of angina.⁸

An nitroglycerin-based paste is frequently used as a preoperative medication in patients with coronary artery disease. A one- to two-inch strip of paste is applied approximately one hour prior to surgery along with other premedicant drugs. Any patient with underlying heart disease who receives anesthesia with nitrous oxide *must* have the percentage of oxygen delivered in the gas mixture monitored carefully.

Specific Anesthetics for Patients with Coronary Artery Disease

It is extremely difficult to always determine the relative safety of general vs. regional vs. local anesthesia in patients with ischemic heart disease because the more extensive procedures are almost always performed under general or regional anesthesia, and the less extensive procedures are done under local anesthesia. One study indicates that in patients with coronary artery disease, there is a 32.0% incidence of complications with general anesthesia, a 27.0% incidence with spinal anesthesia, but only a 1.5% incidence of complications under local

anesthesia.⁹ However, it was noted that the procedure were quite different among the various types of anesthesia.

Nitrous Oxide

In vitro studies show that nitrous oxide is a direct myocardial depressant. This effect is reversed by calcium.¹⁰ Clinical studies concerning the effect of nitrous oxide on the patient with coronary artery disease indicate varied results. Eisele and coworkers¹¹ administered nitrous oxide to patients after they had undergone cardiac catheterization for suspected coronary artery disease (CAD). They found that myocardial function was depressed by nitrous oxide in those patients with angiographically documented CAD but was unaltered in those with angina but no CAD. Therefore, nitrous oxide should be used with care in the patients with CAD.

Diazepam

In both the oral and intravenous form, diazepam is extremely useful in relieving anxiety. When given in very large doses (e.g., 20-30mg IV), this drug causes a significant vasodilation and a decrease in arterial blood pressure.¹² However, in smaller doses, this problem is not significant even in patients with underlying cardiac disease.

Narcotics

In small doses, none of the narcotics (morphine sulfate, meperidine hydrochloride, or fentanyl) have significant adverse effects on the patient with coronary artery disease.

Vasoconstrictors Included in Local Anesthetic Solutions

Controversy exists concerning inclusion of vasoconstrictors in the local anesthetic agents used for dental procedures. This concern stems from the extreme variability of methods used in studies as well as a broad range of cardiovascular effects noted with different doses of epinephrine. A frequently quoted but uncontrolled retrospective study¹³ indicates that epinephrine is safe for use in dental practice in patients with heart disease. However, the ultimate answer to the safety of vasoconstrictors (especially epinephrine) in patients with cardiovascular disease awaits more definitive data from a comprehensive, prospective study in patients with known cardiac disease in which clinically useful dosages of epinephrine are used.

If vasoconstrictors are necessary, care should be taken to use the smallest effective dose.

Conclusions

Historical data concerning the signs and symptoms of ischemic heart disease should be sought from all adults. An in-depth history should be obtained from men over 40 and postmenopausal women. A complete list of medications should be obtained; when not available, consultation with the physician or pharmacist is sound practice.

Elevation of blood pressure and heart rate are extremely important in increasing myocardial oxygen demand

and causing myocardial ischemia. Routine vital signs such as heart rate and blood pressure obtained by cuff should be monitored carefully in these patients at risk.

Patients with a history of uncontrolled blood pressure, a myocardial infarction within 6 months, or a history of progressive chest pain with exercise should not have elective surgical procedures until fully evaluated by the primary physician or cardiologist.

Consideration should be given to electrocardiographic monitoring of patients with ischemic heart disease undergoing extensive dental procedures.

Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used.

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Asociación Puertorriqueña del Corazón

La Asociación Puertorriqueña del Corazón ofrecerá el Curso: "Electrocardiografía Avanzada: Del Laboratorio de Electrofisiología al Electrocardiograma de Superficie" durante los días 10 al 12 de febrero de 1989 en el Hotel San Juan de Isla Verde.

El curso será dictado por el prominente electrofisiólogo, Dr. Pedro Brugada, Profesor Asociado y Director del Laboratorio de Electrofisiología de la Universidad de Limburg en Maastricht, Países Bajos.

El curso estará acreditado por 20 horas de Educación Médica Continuada y diseñado exclusivamente para Cardiólogos. *La matrícula estará limitada a 60 inscripciones* y el costo de la misma será de \$250, el cual incluirá 3 almuerzos y 5 recesos para tomar café. El curso comenzará diariamente a las 8:30 a.m. y terminará a las 5:00 p.m., excepto el domingo que concluirá a las 4:00 p.m.

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Endurance Training and the Prevention of Coronary Heart Disease*

Wildor Hollmann, MD**

The functional basis of heart infarction is a disproportion between oxygen demand and oxygen supply in the myocardium. How can physical training help to prevent this situation? The quality of training must be evaluated on the basis of five fundamental components of physical strain: coordination, flexibility, strength, velocity, and endurance. Every kind of strain causes a different acute reaction and chronic adaptation. Only the effects of endurance training are considered here.

General aerobic endurance training

There are eight different grades of endurance training of which the general aerobic is the most important one. It involves the dynamic work of large muscle groups for at least 30-40 mins, 3-4 times per week, at the limit of the individual aerobic-anaerobic threshold as determined by using the criterion of 2-4 mmol/l lactic acid in the arterial blood. The intensity of exercise can be judged by pulse frequency: 130 to 160/min in healthy males and females below age 50; for healthy subjects older than 50, the following rule of thumb can be applied: 180 minus age in years = pulse rate when training.

Recommended sports are jogging (very slowly), bicycling, cross-country skiing (very slowly), uphill walking, swimming (more than 300-400 m), ball games such as tennis, soccer, basketball, hockey (not recommended: volleyball, table tennis, squash), rowing and canoeing.

Biochemical and biophysical adaptations

In trained *skeletal muscle* we can differentiate between metabolic and haemodynamic adaptations. The metabolic alterations are: an increase in the number and size of mitochondria; increased activity of some aerobic and anaerobic enzymes; an increase of myoglobin; an increase of intramuscular glycogen content; a lowering of the insulin level.

The peripheral haemodynamic adaptations consist mainly of increased capillarization, i.e. enlargement of the capillary surface. It is still unclear to what degree collateral vessels can be developed.

The importance of these adaptations in trained skeletal muscle can be seen in a reduction of sympathetic impulses to the heart. This can be proved by an endurance training

of one leg on a bicycle ergometer. After six weeks of such training the subject's heart rate during exercise will be significantly lower at a given submaximal work load when performed with the endurance-trained leg. No marked difference can be noted when the untrained leg is used. The respiratory minute volume shows the same tendency: it is significantly lower at a submaximal work load when the trained leg is used.

The improved peripheral training condition results in a reduction of the myocardium's oxygen demand, for which the heart rate is the most important factor.

The main adaptations of the *heart* are: reduction of the heart rate at rest and at submaximal work loads; prolongation of the diastolic phase; enlargement of the stroke volume; decreased catecholamine release; greater electrical stability of the heart muscle.

Most of these factors reduce the myocardial oxygen demand. Further, the prolongation of the diastolic phase results in improvement of myocardial blood supply.

Many important preventive effects of endurance training can be detected in the *blood*. The rigidity of the erythrocytes membrane increases. This reduces capillary resistance and improves the blood's flow properties. At the same time adhesiveness and aggregation of platelets decrease, thus opposing thrombosis.

The alterations of *lipid metabolism* induced by endurance training are very interesting. HDL increases, especially the important HDL₂ fraction; LDL cholesterol and the amount of neutral fats decline; and the activity of some important enzymes shows favourable changes.

The practical importance of these changes has been shown by Kramsch et al. (1981) in experiments with *anthropoid apes*. Forty eight animals were divided into two groups: one performing jogging comparable to the above mentioned programme, the other leading a normal life. Both groups had the same diet causing severe arteriosclerosis. After two years, seven of the untrained animals had died of myocardial infarction. The surviving animals were killed and autopsied. The endurance-trained animals had far bigger coronary artery volumes and substantially less arteriosclerotic changes in the coronary walls, their HDL levels were much higher and their LDL levels lower. The Kramsch experiments are important since similar studies cannot be performed on humans for obvious reasons.

In corresponding experiments we were able to show that the cardiovascular adaptations to endurance training are even found in healthy subjects aged between 55 and 70 years. Within 12 weeks even the group of the 65-70 year-olds had regained a cardiopulmonary capacity equalling the average one of untrained persons 20 years younger. The main reason was a larger stroke volume of

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the heart at rest and under submaximal work loads on the bicycle ergometer. The heart volume was unchanged. Biopsies of the *m. vastus lateralis* showed a significant increase in the number of mitochondria and of some aerobic and anaerobic enzymes. The capillary surface increased significantly. If one day we could have a drug that reduces myocardial oxygen demand, increases the blood supply, stabilizes the electrical activity of the heart muscle, improves the flow properties of the blood and has an anti-thrombotic effect at the same time, elevates the HDL and reduces the LDL level and brings all these changes about without undesired side effects— what worldwide enthusiasm this would cause!

The results of Paffenbarger et al. (1978) and Morris et al. (1981) demonstrating a significantly lower risk of myocardial infarction in endurance-trained subjects are understandable, but it is not possible to establish the definite importance of endurance training for preventive cardiology as this would require a double-blind trial,

which is both impractical and unethical.

Physical exercise is contraindicated in organically healthy persons with a full stomach or when the body temperature is raised.

Special caution is necessary under the following conditions: environmental temperatures of more than 28°C; a relative air humidity of more than 80-85%; on arrival by lift or mountain railway at altitudes of more than 2,500m the body should be allowed approximately 10 minutes to adapt itself to the lower partial pressure of oxygen in the respiratory air before extensive exercise is started.

Finally it can be stated that a healthy life style and physical training give a relative protection against acute cardiovascular catastrophes. There is no absolute protection but physical training will keep you functionally—though not biologically— younger than your birth certificate says, and thus you may die “young” at an old age.

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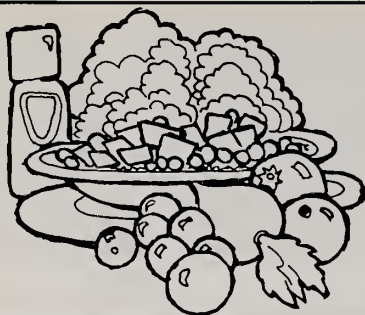
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MEDICAL ASPECTS OF NUTRITION

The Surgeon General's Report on Nutrition and Health*

Marion Nestle, PhD, MPH**

The Surgeon General's Report on Nutrition and Health,¹ released in July 1988, is the latest addition to federal dietary guidance for the general public. This 712-page report represents the culmination of four years of effort by the U.S. Public Health Service. It provides a comprehensive review of the scientific evidence that links diet to health, along with consensus recommendations for changes in dietary intake and public health policies based on that evidence.

The prestige of the Surgeon General and the Public Health Service, the comprehensive scientific review and the elaborate process used to achieve consensus on the conclusions and recommendations make this report of unusual interest and impact. The report's principal conclusion—that reduction of fat intake is the primary priority for dietary change—suggests the desirability of a nationwide effort to reduce the overall fat intake of Americans.

Genesis of the Report

The major impetus for development of *The Surgeon General's Report on Nutrition and Health* derived from recognition that dietary guidance needed to reflect the shift in nutritional priorities in the United States from problems of nutrient deficiencies to those associated with dietary overconsumption. In the early years of this century, federal dietary recommendations encouraged consumption of foods containing fat and sugar and assigned foods to groups in order to promote a more varied diet and to prevent nutrient deficiencies.² This advice did not distinguish foods of high- and low-fat content nor did it suggest the need for limitations on intake of any type of nutrient.

Advice changed as it became evident that leading causes of death in the United States were associated with

diets too high in fat, calories, salt and alcohol, and too low in fiber. The 1977 U.S. Senate report, *Dietary Goals for the United States*,³ the first federal publication to emphasize these associations, was soon followed by *Healthy People: the Surgeon General's Report on Health Promotion and Disease Prevention* in 1979,⁴ and the first edition of the *Dietary Guidelines for Americans* in 1980.⁵

Magnitude of the Problem

The driving force behind these reports was the magnitude of the impact of diet-related disease on the health of Americans. Among the ten leading causes of death in the U.S. are five—coronary heart disease, certain types of cancers, strokes, diabetes mellitus and atherosclerosis—that have been associated with diet and three others—accidents (especially motor vehicle), suicides, and chronic liver disease and cirrhosis—associated with alcohol consumption. Together, these conditions account for nearly 70% of the more than 2 million annual deaths in this country.⁶

Diet, of course, is not the only influence on these diseases of complex etiology and the proportion of illness and death that can be attributed directly to dietary factors has never been established. Nevertheless, the prevalence of these problems suggests that even a small reduction in their risk would produce substantial health benefits to the population.

Development of the Report

To meet the government's responsibility to provide dietary advice to the public based on an authoritative analysis of available research information, the Assistant Secretary for Health in 1984 assigned the task of preparation of a *Surgeon General's Report* to the Nutrition Policy Board of the Department of Health and Human Services (DHHS). Chapters were delegated to Public Health Service Agencies. Each chapter was designed to identify the most important research issues related to diet and disease, review current understanding of those issues and evaluate the implications of this knowledge for public

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health policies in nutrition education, programs and services, and research and surveillance.

Evaluation of the scientific base was accomplished by more than 50 scientists in government and the private sector who drew on information reported in more than 2,500 research studies. To develop a consensus on the policy issues and recommendations, each chapter was subjected to six stages of review and revision. Three of these stages were internal reviews by Public Health Service scientists; the other three were external reviews by scientists and professionals in the private sector. In addition, three separate committees reviewed the entire report at one or more stages of preparation. In sum, more than 200 nutrition professionals were involved in review of the report. To achieve the final consensus, representatives of Public Health Service agencies met in day-long conferences to review chapters line by line.

Conclusions and Recommendations

The result of this extraordinary effort is a report that examines a wide range of dietary issues related to many different disease conditions. Its principal conclusions are:

1. Excesses and imbalances in intake of dietary factors can increase the risk of chronic diseases.
2. Dietary changes can improve the health of Americans.
3. The primary dietary priority is reduced consumption of fat, especially saturated fat.
4. Similar dietary recommendations apply to prevention of essentially all diet-related chronic diseases.

The report's nine dietary recommendations are summarized in the Table. Five of these recommendations apply to the general public; four apply only to specific population groups. Thus, the *Surgeon General's Report* extends previous recommendations in three ways: it distinguishes the targets of recommendations, it designates fat reduction as the primary priority and it emphasizes the universality of its dietary recommendations for prevention of chronic disease.

Policy Implications

The report states the implications of its findings and recommendations for a broad range of public health policies. In *dietary guidance*, it improved education of the public about dietary choices most conducive to good health (especially among groups at greatest risk), improved use of nutrition labels to help consumers identify foods that meet dietary recommendations and improved nutrition education for physicians and other health professionals.

For *nutrition programs and services*, it recommends identification and removal of the barriers to optimal health and nutritional status among high-risk groups, incorporation of nutrition services into all health-care programs, increased availability of low-fat foods products, access to an appropriate diet for all Americans and adherence of food service and assistance programs to the principles of good nutrition stated in this report.

In the area of *research and surveillance*, the report recommends improved monitoring of nutritional status among high-risk groups, expanded research investiga-

Table

Summary of the Recommendations Issues for Most People

Fats and cholesterol: Reduce consumption of fat (especially saturated fat) and cholesterol. Choose foods relatively low in these substances, such as vegetables, fruits, whole-grain foods, fish, poultry, lean meats and low-fat dairy products. Use food preparation methods that add little or no fat.

Energy and weight control: Achieve and maintain a desirable body weight. To do so, choose a dietary pattern in which energy (caloric) intake is consistent with energy expenditure. To reduce energy intake, limit consumption of foods relatively high in calories, fats and sugars, and minimize alcohol consumption. Increase energy expenditure through regular and sustained physical activity.

Complex carbohydrates and fiber: Increase consumption of whole-grain foods and cereal products, vegetables (including dried beans and peas) and fruits

Sodium: Reduce intake of sodium by choosing foods relatively low in sodium and limiting the amount of salt added in food preparation and at the table.

Alcohol: To reduce the risk for chronic disease, take alcohol only in moderation (no more than two drinks a day), if at all. Avoid drinking any alcohol before or while driving, operating machinery, taking medications or engaging in any other activity requiring judgment. Avoid drinking alcohol while pregnant.

Fluoride: Community water systems should contain fluoride at optimal levels for prevention of tooth decay. If such water is not available, use other appropriate sources of fluoride.

Sugars: Those who are particularly vulnerable to dental caries (cavities), especially children, should limit their consumption and frequency of use of foods high in sugars.

Calcium: Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat-dairy products.

Iron: Children, adolescents and women of childbearing age should be sure to consume foods that are good sources of iron, such as lean meats, fish, certain beans and iron-enriched cereals and whole-grain product. This issue is of special concern for low-income families.

tions into the relationships between specific dietary factors and the chronic diseases, identification of the childhood dietary pattern that best prevents development of chronic disease, elucidation of the nutrient and energy requirements of older adults and identification of effective educational methods to help the public translate dietary recommendations into appropriate food choices.

Implementation Agenda

These policy recommendations are aimed at nothing less than changing the American diet to one that is lower in fat and higher in complex carbohydrates and fiber. To accomplish this difficult task, federal leadership is essential, especially to improve food labels, access to nutrition services, quality of food assistance programs, nutritional status monitoring and professional and public nutrition education. But leadership from the private sector is also essential. Nutrition professionals in government, industry, private organizations, schools, clinics and communities must all take responsibility for this effort if it is to succeed.

The ultimate targets for change are individuals and their food choices. Because individuals make food choices within the context of their cultures, changes also

must occur in the major societal influences on diet—advertising, market availability, information from the media, point-of-purchase information and advice from professionals. The challenge posed by the *Surgeon General's Report* to government, the food industry and the nutrition profession is to create an environment favorable to individual choice of healthier diets.

Summary

The most important accomplishment of the *Surgeon General's Report* is its establishment of a sound scientific basis for dietary recommendations for chronic disease prevention. From this foundation, all levels of government, the food industry and the nutrition profession should be able to develop programs and policies that put dietary recommendations into common practice.

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The work reported here was conducted while Dr. Nestle was Staff Director for Nutrition Policy, Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, DC.



**Sirviendo al Pueblo
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Find the time.
Have a mammogram.



Discurso de Toma de Posesión del Dr. Calixto E. Pérez Prado como Presidente de la Asociación Médica de Puerto Rico

Para mí es un privilegio ser un eslabón más de una larga cadena de distinguidos médicos, que me han precedido en este honroso cargo, para servir a nuestra Asociación, a la profesión médica y a los necesitados de nuestros conocimientos y servicios, que es el pueblo de Puerto Rico.

Con humildad, respeto y entusiasmo, acepto el honor que me hacen ustedes, los líderes de nuestra profesión en Puerto Rico, para presidir esta augusta y prestigiosa Asociación Médica.

Al dirigirme a ustedes, me comprometo a continuar la política pública establecida por nuestra Asociación a lo largo de su trayectoria histórica. Deseo que nada quede en el pasado, y le daré continuidad a todos aquellos asuntos de importancia iniciados en los últimos años, y que hasta el presente no han sido concluidos.

Seguirá de primera importancia solucionar la discriminada intervención de los planes de seguros médicos en la prestación de servicios por parte del médico a sus pacientes. Sabemos que el médico tiene que intervernir, individual y colectivamente, en la disponibilidad de cubierta médica, decidir sobre procedimientos permitidos o incluídos, y el pago de tarifas por servicios prestados.

La querella elevada ante el Comisionado de Seguros está pendiente de dirimirse. No obstante, hemos aceptado reanudar el diálogo con Triple S. Esperamos establecer las bases para futuras relaciones. De la actitud y la disposición de la Junta de Directores de Triple S y su interés por resolver nuestras diferencias, dependerá la acción a seguir por la Asociación Médica de Puerto Rico.

Aún así seguiremos estudiando y considerando el establecimiento de un plan de servicios de salud por la Asociación Médica.

Continuaremos los esfuerzos ya iniciados para que las agencias federales consideren nuestros reclamos de una retribución justa por los servicios prestados por los médicos en Puerto Rico a pacientes del Programa de Medicare y que se equiparen con áreas equivalentes en los otros estados de la nación. A la misma vez, estaremos atentos a los resultados y recomendaciones del estudio de Harvard sobre la retribución por escala de valores relativos y basada en costos de recursos.

En reunión extraordinaria, la Cámara de Delegados aprobó la propuesta de reglamento, que da vigencia a la encomienda de reglamentación y evaluación de la práctica de la medicina, otorgada a nuestra Asociación por el Honorable Secretario de Salud, según consigna la Ley 11 de 1976. Este reglamento será considerado por el Consejo General de Salud, sometido a vistas públicas y, de ser aceptado, será firmado por el Secretario de Salud.

Nuestra Asociación tendrá la facultad de autorreglamentar nuestra profesión y controlar la calidad de la práctica de la medicina en Puerto Rico. Esto requerirá que se establezca la organización y se provea el personal y financiamiento necesario.

Tenemos que asegurarnos que el control de la excelencia de la práctica de la medicina la tengamos los médicos, a través de nuestra Asociación. En el proceso de evaluación que otorga este reglamento deseamos y queremos la participación de todos los médicos de Puerto Rico, preferiblemente, uniéndose a nuestra Asociación.

Continuar con el fortalecimiento de nuestra Asociación es de vital importancia. Hemos logrado recientemente proyectar una imagen de mayor preocupación por los problemas en el campo de la salud, y los que se relacionan con la profesión médica. Hemos creado un vehículo de comunicación para llegar a todos los médicos y entidades relacionadas con la salud al darle realidad a nuestro periódico Prensa Médica. Entendemos que este vehículo de comunicación, junto a una oficina de relaciones públicas eficiente y activa, será un factor importante en fomentar la unión y el deseo de pertenecer a nuestra Asociación, de todos los médicos de Puerto Rico. Necesitamos que llegue el mensaje de que nuestra Asociación sí hace por los médicos, sí sirve a los médicos y sí defiende a los médicos de Puerto Rico; pero que también está para defender a los pacientes, que son la razón de existir del médico, y para velar por el bienestar y la salud del pueblo de Puerto Rico.

Es motivo de satisfacción el desarrollo del sistema computarizado, que junto a una reorganización administrativa habrá de impartir mayor agilidad a nuestra organización para responder a las necesidades de nuestra matrícula y facilitar el que la administración, Junta de Directores, Consejos y Comités, cuenten con los elementos necesarios para desarrollar su actividad al máximo, y sobre todo, a tiempo.

Hemos de continuar la campaña de reclutamiento de nuevos socios, y daremos énfasis al atraer a los médicos recién graduados, así como a los estudiantes de las escuelas de medicina. Pido a los presidentes de las Sociedades de Distritos y Secciones de Especialidades de la Asociación, que nos unamos en una campaña vigorosa y activa de reclutamiento de nuevos socios. Recordemos que es necesario el tener una voz única y fuerte que nos defienda.

Nombraremos un comité para trabajar en la búsqueda de nuevas áreas de servicio a los socios, tales como asesoramiento en finanzas, descuentos en seguros, descuentos en compras, adiestramiento de personal de oficinas médicas y otros beneficios que sirvan de

atractivo económico para los socios. Nos proponemos, además, dar atención en particular a la problemática de los médicos en el servicio público. Esta será una encomienda específica para el Consejo de Medicina de Gobierno, que luego de estudiar a fondo las dificultades de estos compañeros de profesión, deberá traer recomendaciones y soluciones que proponer a las agencias concernidas.

Como es de su conocimiento, la revisión global y enmiendas a nuestro reglamento, quedó pendiente al finalizar el año. En breve, el Consejo Judicial habrá de presentar sus recomendaciones a la Cámara de Delegados. Será de prioridad para esta Junta y su Consejo Judicial, el poner en efecto —lo antes posible— lo dispuesto en sus enmiendas.

Estaremos atentos a otros asuntos que hasta el presente no han finalizado.

En el área de responsabilidad profesional se logró que el Sindicato comenzase a emitir pólizas, y al presente cuenta con 758 médicos asegurados. Además, el que otras compañías como Triple S y Cooperativa de Servicios Múltiples, hayan entrado al mercado, ha mejorado el cuadro. Aún así, deben considerarse otras soluciones con más estabilidad y que no estén sujetas a vaivenes del mercado, como son el “no fault” y el “Tort Act Reform”. Encomendaremos este estudio a los organismos pertinentes de nuestra Junta de Directores.

En el pasado —y muy particularmente en los últimos tres años— hemos vivido la agotante experiencia de reaccionar a legislación sobre temas de salud que afectan a nuestra profesión y que surgen de otras esferas, respondiendo a otros intereses. Seamos de avanzada. Es hora ya de asumir el liderato en toda legislación sobre la profesión médica y la salud del pueblo.

El Consejo de Política Pública, y el de Medicina de Gobierno, tendrán la encomienda de analizar toda el área de legislación, tanto en la medicina privada como de gobierno, y recomendar acción y legislación pertinente. Esperamos mantener y fortalecer las buenas relaciones logradas en el ámbito ejecutivo y legislativo del gobierno, y muy en particular con el Secretario de Salud, para lograr nuestros propósitos en esta gestión.

La demostración de liderato y despliegue de fuerza de nuestra Asociación en el pasado año, además de costar un esfuerzo inusitado de todos los directivos y de numerosos socios, conllevó erogaciones por encima de nuestros recursos. Ha quedado demostrada la necesidad de mayores ingresos para mantener el mismo nivel de ejecución, no ya de aumentarlo, como creemos necesario y proyectamos. No podemos escapar a la realidad de que nadie está obligado a proveer esos recursos, sino nosotros mismos. Tenemos que pagar el costo de defender nuestra profesión. Con el propósito de explorar nuevos mecanismos de financiamiento, habremos de nombrar un comité bajo la presidencia del doctor Gerardo Martorell, Presidente Electo, que utilizando el conocimiento de algunos compañeros médicos, así como de personas versadas en el campo financiero, habrán de proponer y ayudar a implantar medidas a corto y largo alcance, para darle a nuestra Asociación una sólida base económica.

De inmediato, y utilizando la habilidad y capacidad profesional del Lcdo. Rubén D'Acosta, estamos formando lo que llamaremos una Oficina de Proyecciones Económicas. Esta oficina se dedicará todo el tiempo a gestionar aumentar los ingresos de actividades ya utilizadas en el pasado, y a crear nuevas alternativas.

La idea, ya esbozada en conversaciones con el doctor Buonomo sobre la creación de un fideicomiso mediante aportaciones de todos los médicos conscientes de esta necesidad, es merecedora de desarrollarse de inmediato. Esta idea requiere la participación activa de los líderes de los Distritos, pues será necesario el contacto personal con todos los médicos de Puerto Rico.

Hay muchos otros asuntos y dilemas que están en el ambiente y que deben preocuparnos como profesión. Más aún debemos y tenemos que exigir participación activa como representantes de la medicina organizada en la consideración y solución de asuntos tales como costo y calidad de los servicios médicos, competencia profesional, disponibilidad de servicios y otros más. Muy en particular el mejoramiento de la calidad de vida de nuestro pueblo y la preservación de la calidad ambiental para el disfrute de la vida del puertorriqueño, habrán de ser atendidas al máximo de nuestras posibilidades.

Espero aportar el máximo de mi esfuerzo para conseguir lo que a grandes rasgos he presentado a ustedes. En la misma medida que me he comprometido a darle continuidad al quehacer de nuestra Asociación, así espero que los que me sigan acepten este reto. Tenemos que aceptar el llamado del deber para legar a las nuevas generaciones de médicos un ambiente en donde tengan la autoridad de hacer decisiones en favor de sus pacientes, con responsabilidad plena y a tono con las realidades apropiadas.

Necesitamos urgentemente llevar el mensaje y convencer a los médicos de Puerto Rico que su adhesión y participación en la Asociación Médica es indispensable. A través de nuestra fuerza de grupo, la reglamentación propia y la conciencia del deber para con nuestros pacientes, tenemos que dejar sentado que estamos al timón, que es el médico el responsable y a la vez el que tiene que decidir qué es y cómo se practica la mejor medicina del mundo para los puertorriqueños.

Que Dios nos ayude a descargar esta responsabilidad.

NOTA BIOGRAFICA



DR. CALIXTO E. PEREZ PRADO

Nacido en Vega Baja, Puerto Rico, el 14 de octubre de 1931. Su padre, Emilio Pérez Alonso y su madre, Blanca Prado Guerrero. Su esposa Migdalia, y sus hijos Emilio Alberto, cirujano general; Gilberto Luis, dentista; Migdalia Amara, patóloga del habla; y Blanca Emilia, bachiller en administración con maestría en mercadeo.

Cursó estudios secundarios en la Escuela Superior Central de Santurce (1949). Bachillerato en Ciencias en la Universidad de Puerto Rico en el 1952. Graduado de medicina en la Escuela de Medicina de la Universidad de Puerto Rico en 1956. Realizó su internado en el antiguo Hospital de Distrito de Bayamón del 1956 al 1957. Obtuvo una Maestría en Salud Pública en la Escuela de Salud Pública del Recinto de Ciencias Médicas (1958-1959). Estudios de Administración de Hospitales en Columbia Presbyterian School en 1961. Residencia

en Medicina Física y Rehabilitación en el Hospital Universitario del 1967 al 1969.

Fue director Auxiliar de la División de Hospitales del Departamento de Salud, del 1959 al 1961. Director Regional del Departamento de Salud, Región Este (Fajardo), del 1962 al 1967. Director del Departamento de Medicina Física y Rehabilitación del Hospital Regional de Caguas durante los años 1970 al 1986. Práctica privada de Fisiatría en Caguas desde el 1970 al presente.

Es miembro de la Asociación Medicina de Puerto Rico desde 1967. Desempeñó posiciones electivas en dicha Asociación, tales como presidente de la Sociedad Médica del Distrito Central y Vicepresidente, Tesorero, Presidente de la Cámara de Delegados y Presidente del Comité de Finanzas de la Asociación Médica de Puerto Rico.

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POR LA TARDE 764-9056
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2. CRYOCIRUGIA
3. SONICAD DOPPLER
4. SPECULUM
5. PESA
6. MESA DE RECONOCIMIENTO
7. ESTERILIZADORA
8. ARCHIVERO HORIZONTAL
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858-6077.

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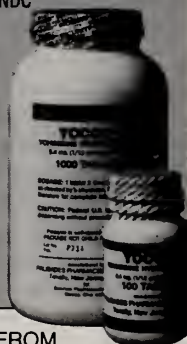
Dosage and Administration: Experimental dosage reported in treatment of erectile Impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

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PREVENTING ALCOHOL-RELATED INJURIES AND FATAL ACCIDENTS

Physicians treating motor vehicle injuries must be more willing to diagnose patients with a drinking problem and refer them for treatment, says a study in the *Journal of the American Medical Association*.

Failure to do so may eventually lead to the passage of laws mandating blood alcohol testing of patients injured in motor vehicle accidents and the involvement of public health authorities in the assessment and treatment of those injured while intoxicated, say the study's authors, Grace Chang, MD, MPH, and Boris M. Astrachan, MD, of the Yale University School of Medicine, New Haven, Conn.

In a study of 320 patients who received emergency treatment for motor vehicle injuries, the authors found 80 (25 percent) had had blood alcohol levels measured. The authors predicted and found that the rate of alcohol testing was the same before and after June 1986—when a new law went into effect in Connecticut that deciding whether a person had been driving while intoxicated.

The patients in the study who had been tested were those who had been more seriously injured, and testing was done primarily because of immediate medical need, not for case-finding, the authors report. While 27 tested negative, 53 had levels ranging between 50 and 550 mg/dL, and 47 were equal to or above the 200 mg/dL median score—the level a 160 lb. person would reach by drinking seven to eight martinis or eight 12-oz. bottles of beer on one hour on an empty stomach.

In an accompanying study, researchers at the Centers for Disease Control (CDC), Atlanta, found a strong dose-response relationship between the number of drinks a person says he or she usually consumes per occasion and the likelihood of dying an accidental death. The risk of fatal injuries nearly doubles for those who say they usually consume five drinks and more than triples for those who report imbibing nine alcoholic beverages per occasion, the authors say.

Motor vehicle accidents are the single most important cause of injury in the United States, accounting for nearly 50,000 deaths and 4 to 5 million injuries yearly, the Yale researchers write. Studies show blood alcohol concentra-

tions of 50 mg/dL are associated with an increased risk of injury-causing auto accidents, and driving skills are seriously impaired by levels above 100 mg/dL.

Despite the evidence of serious drinking problems, none of the study subjects who tested positive had been referred for evaluation or treatment, Chang and Astrachan report. The failure to address a probable drinking problem may be caused in part by what they call the "pernicious attitude of defeatism about alcohol management." Despite evidence that treatment success rates "can be as good as or better than those for many medical problems, alcoholics are permitted to use medical centers as revolving doors, with the witting and unwitting complicity of institutions." They conclude that all motor vehicle accident patients should be evaluated for alcohol abuse and referred for treatment if a drinking problem exists.

In the CDC study, data was obtained from 13,251 adults in the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, say the authors, Robert F. Anda, MD, MS, and colleagues. During the mean follow-up period of 9.3 years, 81 persons died from accidental injuries, they say. Overall, 7.1 percent of the cohort said they usually consume five or more drinks per occasion. This group was 1.9 times more likely to suffer fatal injuries in the follow-up period than those who drank less. The risk was 3.3 times greater for those who claimed to imbibe nine or more drinks. The authors conclude that self-reported alcohol consumption may serve as a significant indicator for risk of fatal injuries.

"We can now fulfill the three necessary criteria for preventive counseling about alcohol," writes Julian R. Waller, MD, MPH, of the University of Vermont College of Medicine, Burlington, in an accompanying editorial. "We have information that allows us to predict a relationship between alcohol consumption and injury risk; this information can be communicated easily during the usual office visit; and we have evidence that patients who are provided with this information will act to reduce their risk," Waller concludes.

JAMA November 4, 1988

ALCOHOLICS NOT POOR CANDIDATES FOR LIVER TRANSPLANTS: REPORT

Alcoholic patients with cirrhosis are just as likely to benefit from liver transplantation as adults with other liver diseases, since undergoing the traumatic procedure leads to abstinence and rehabilitation in most cases, says a report in the *Journal of the American Medical Association*.

The report, by Thomas E. Starzl, MD, PhD, and colleagues at the University of Pittsburgh, is a review of 35 patients with alcoholic cirrhosis, who received transplants between 1963 and June 1987 and who survived six months or longer. Of these, only two returned to alcohol

abuse, the authors say.

The use of liver transplants to treat alcoholic cirrhosis has been criticized by health care professionals and even prohibited by health care funding agencies, the authors say. "To the extent that objections to liver transplantation are moralistic, these undermine the modern understanding of alcoholism including the recognition that this is a treatable disease, not a vice."

The fact that relapses of alcoholism have been uncommon after hepatic transplantation weakens the objection that provision of a new liver is a futile gesture and a waste of a potentially life-saving organ. The traumatic experience of liver transplantation appears to lead the patients almost invariably to long or permanent abstinence and rehabilitation, the authors write. "Our only relapses were in two patients who, after transplantation, appeared to resent what had been done while they were in a coma or mentally incompetent. Thus, the will of the patient to live may be the most important selection factor. Not far behind may be an explicit admission of alcoholism by the patient and this family and an expression of determination to effect behavioral change."

Before the immunosuppressive drug cyclosporine became available, 15 alcoholics received liver transplants, with only four long-term survivors. "The three surviving patients are in good health with normal liver function after 14, 11 1/2, and 11 years, respectively." One patient—who unconscious when the decision was made for transplantation and had been "angry at having been rescued"—returned to drug abuse and drinking and died of pneumonia 4 1/2 years after the transplant.

Of the 41 transplants performed since cyclosporine became available in 1980, 28 (68.3 percent) are still living. The authors report no significant difference between their survival rate and that of 625 adults who received transplants for other causes of end-stage liver disease. Of the 30 recipients who survived at least six months, only one resumed drinking. This patient also was unconscious when the transplantation decision was made and his family refused to accept the diagnosis of alcoholism then or later.

"A remarkable record of rehabilitation was established by the 30 patients in the cyclosporine era who survived at least six months," the authors report. "Twenty-seven returned to jobs or fully maintained their households." Of the three who didn't resume employment, one was disabled with back pain, one retired, and the other was dysfunctional because of borderline mental retardation.

"Since 1980, the results with alcoholics patients have been as good as in adult patients with a broad spectrum of other hepatic diseases," they say. "In fact, the results have been better than with diseases that can recur in the transplanted liver such as type B hepatitis, hepatic malignancies, and Budd-Chiari syndrome."

The authors also argue against the imposition of any arbitrary period of abstinence before transplantation. Such a waiting period would seem medically unsound or even inhumane since it would allow a patient's medical condition to seriously deteriorate and reduce his or her chance of survival, they write.

JAMA November 4, 1988

OBESITY TREATMENT IN ADULTS

A comprehensive, long-term weight-control program incorporating diet, exercise, and behavior modification is the only effective treatment for obesity, says an AMA report in the *Journal of the American Medical Association*. These factors are "interdependent and mutually supportive," so a program including all three is more likely to lead not only to weight loss but to maintenance of weight loss, says the report by the AMA's Council on Scientific Affairs (CSA). "Concern with weight control should begin sufficiently early in life to reduce the risk of developing obesity. The complex etiology of obesity is, in part, responsible for the difficulty physicians encounter in treating this condition. Prevention is the 'treatment' of choice," the CSA says. It also suggests that an evaluation of a commercial weight-loss clinic should include a determination that "the proposed weight-loss program is appropriate for the individual's physical condition" and that proper medical supervision is provided by knowledgeable physicians.

JAMA November 4, 1988

PROBLEMS WITH NON-INVASIVE, 24-HOUR BLOOD PRESSURE MONITORS

Non-invasive, 24-hour ambulatory blood pressure monitors are widely used in the United States in studies of new hypertension drugs, and increasingly used in diagnosing, treating and monitoring high blood pressure. But a letter in the *Journal of the American Medical Association* suggests some caution in using these microprocessor-controlled monitors. The authors, James F. Burris, MD, of the Cardiovascular Center of Northern Virginia, Falls Church, and colleagues, report seeing a number of complications in four patients using the devices over the past year. Problems included swelling of the hand, abrasions, and bruises, skin inflammation, and tiny subcutaneous hemorrhages at the blood pressure cuff site. There have been two previous reports of similar or related problems, the letter notes. In two cases, complications were associated with monitor malfunctions, but the rest occurred with normal use. These monitors, "should, as with any medical device, be used with some caution, although complications seem to occur infrequently," the letter concludes.

JAMA November 4, 1988

CLINICAL ETIQUETTE

In the rush to teach new doctors the facts and skills of their profession, "how the physician should deport himself or herself is all too often neglected," a commentary in the *Journal of the American Medical*

Association says. The author, Thomas W. Furlow, Jr., MD, of the Walter Reed Army Medical Center, Washington, DC, offers some suggestions on clinical etiquette, the manner and style in which the physician should interact with the patient. He advises such things as conservative dress, moderate and careful grooming, sensitivity in communication, and courtesy and respect in bedside manner. While a physician's clinical skill is key to building trust with a patients, "proper conduct and observance of the social amenities are the polished ornaments that adorn the physician's presence and bedside manner," Furlow writes. "To my mind, there is no civilized reason why such ornaments should not always be on display."

JAMA November 4, 1988

PROPRANOLOL TREATMENT FOR CHILDREN WITH ACUTE POSTTRAUMATIC STRESS DISORDER

The beta-blocker propranolol, prescribed for hypertension and other conditions, also may help treat symptoms of acute posttraumatic stress disorder (PTSD) in children, suggests a pilot study in November's *American Journal of Diseases of Children, AJDC*. The report, by Richard Famularo, MD, of the Harvard Medical School, and colleagues, involved 11 children aged 6 to 12 who were victims of physical and/or sexual abuse and exhibited moderate to severe PTSD symptoms. Symptoms improved while the patients were on propranolol and worsened when they were taken off, the authors report. Some of the improvement likely was due to a placebo effect, the authors note. They also acknowledge that drug therapy is not the treatment of choice for PTSD, saying that providing a safe environment, either in an inpatient setting or foster home, is the first step. But "amelioration of the psycho-physiologic symptoms may make individuals more amenable to environmental and psychotherapeutic interventions," they conclude.

PARENTAL LOSS AND DEVELOPMENT OF ADULT PSYCHIATRIC PROBLEMS

The quality of a child's home life following the loss of a parent seems to be a more critical factor in the development of later psychological problems than just the loss itself, a study in the November *Archives of General Psychiatry* suggests. The study by Alan Breier, MD, of the Maryland Psychiatric Research Center, Baltimore, and colleagues also concludes that the reason of the loss—death vs. divorce, for example—doesn't seem to make much difference. The researchers studied 90 adults who lost a parent when they were between 2 and 17 years old. Those adults with a history of psychological problems had a poorer quality of childhood home life

and personal adaption, including a poor relationship with the remaining or surviving parent, following the loss of the parent than did the group with no history of psychiatric disorder. But in an accompanying commentary Christopher Tennant, MD, of the University of Sydney, Australia, takes issue with use of the broad term "parental loss," saying researchers should specify between death and divorce or separation.

CHANGING HOSPITAL BEHAVIOR WITH COMPETITION AND COST-CONTAINMENT

Programs that promote hospital competition along with cost-containment, can dramatically reduce inflation rates for hospital care, a study in the *Journal of the American Medical Association* concludes.

The study examines the behavior of California's hospitals since the enactment of a June 1982 state law allowing selective contracting with hospitals and physicians by both the state Medicaid program and private third-party payers. The legislation was designed to foster cost-reducing competition among health care providers, say the authors, Glenn A. Melnick, PhD, of the UCLA School of Public Health, and Jack Zwanziger, PhD, of The Rand Corp., Santa Monica, Calif.

Previous studies of hospital competition have found that greater competition tends to lead to higher hospital costs, they write. "These results are consistent with the theory that hospital competition, to the extent that it existed, was on a quality basis rather than one of price." California's policies are meant to increase the role of costs in hospital competition behavior.

California's law allows third-party payers to exclude providers from its list of participating health care providers without significant threat of antitrust prosecution. This allows the state Medicaid program and private payers to negotiate discounts with hospitals. This and the Prospective Payment System (PPS) adopted by Medicare in 1983 have had a rapid and substantial impact on California hospitals most susceptible to pro-competition policies, the authors report.

"Hospitals and physicians located in areas with many competitors or substantial excess capacity are more likely to agree to accept lower fees and increased utilization oversight in return for the promise of a continued flow to a continued flow of patients," they write. "Given current national trends... the behavior now observed in California is likely to spread to the rest of the country."

A related *JAMA* study supports this belief. That study, by James C. Robinson, PhD, of the University of California, Berkeley, and Harold S. Luft, PhD, of the University of California, San Francisco, compared the hospital cost-controlling effectiveness of cost-containment policies in Massachusetts, Maryland, New York, New Jersey, and California. While rate-regulation programs, like Medicare's PPS, were found effective in holding down prices, competition appears to work only where hospitals have an incentive to compete on the basis of lower charges.

Overall, hospitals that had to compete with more neighboring institutions had significantly higher costs than those in less competitive markets. But this effect declined between 1982 and 1986, perhaps due to third-party payer cost-control strategies, the authors say. "While hospitals with more than 10 neighbors reported average costs to be 27.5 percent higher than those in comparable hospitals in 1982, they reported costs to be only 23 percent higher in 1986."

In 1982, more competitive hospitals—those with 11 or more neighbors—had average costs 13.3 percent higher than comparable, less-competitive hospitals. By 1986, the most competitive hospitals experienced costs 1.3 percent lower than the least competitive. While California's market-oriented strategy had no cost-reducing effect on hospitals with fewer than 10 neighbors, its overall rate of hospital cost inflation was reduced by 10.1 percent, the authors say.

Melnick and Zwanziger's study provides similar evidence that California's policies are sharply reducing total hospital cost inflation rates. From 1983 through 1985, it says, total inflation-adjusted inpatient costs rose less than 1 percent in hospitals in low-competition markets, versus an 11.29 percent drop in hospitals in highly competitive markets. After controlling for the markets, versus an 11.29 percent drop in hospitals in cost per discharge in highly competitive hospitals was 3.53 percent lower than the rate in low competition hospitals.

The authors of both studies note, however, that more research is needed to determine any impact these policies may have on quality of care, research and education, and medical services for the poor.

JAMA November 11, 1988

STUDYING BRAIN CHEMISTRY WITH PET SCANS

PET scanning, a procedure for examining metabolic activity in the living human brain, is rapidly moving from the research setting into clinical practice, says a report in the *Journal of the American Medical Association*.

No longer just a research tool, PET, or positron emission tomography, is now being used to help doctors diagnose and decide treatment for patients with strokes, epilepsy, brain tumors, schizophrenia, and dementia, says the report by the AMA Council on Scientific Affairs' Positron Emission Tomography Panel.

In an accompanying editorial however, Thomas C. Chalmers, MD, of the Harvard School of Public Health, Boston, cautions against widespread use of the technology before physicians learn which patients can and cannot benefit from PET scans.

PET is an imaging process that displays the degree of activity of a number of important metabolic functions of the brain. In the past, PET scans have been used to study changes associated with disorders seriously impairing mental function. They also have been helping scientists

study how normal and abnormal nerve cells transmit chemical signals, providing insights into the mental functions of thinking, feeling, and behavior, says the council report.

PET's increasing role in research and patient care makes it "one of the most exciting innovations in imaging technology available today," the authors write. It is helping researchers study whether chemical and metabolic abnormalities within the brain account for abnormal mental function and behavior, including delusions, hallucinations, and thought and behavioral disorders, as well as for dementias associated with Alzheimer's, Parkinson's and Huntington's diseases, the report says. Used with other clinical findings, PET scans help doctors decide which epilepsy patients can benefit from surgery. The scans can help locate areas of the brain that trigger the patient's seizures, the surgical resection of which often helps to eliminate or decrease seizure frequency.

PET scans also can delineate the extent of brain tumors and distinguish them from the effects of radiation or other treatments. With conventional radiological imaging techniques, it is often difficult to distinguish between a recurring tumor and radiation-killed tissue. PET scans can show where in the brain glucose is and is not being metabolized—dead brain tissues does not metabolize glucose, while recurrent tumors often exhibit highly active glucose metabolism, the authors write.

By providing measurements of regional blood flow, metabolism, and neurotransmitter and neuroreceptor activity, PET can help distinguish between patients with Alzheimer's dementia caused by blocked blood vessels, and those associated with Parkinson's and Huntington's diseases. "In patients with stroke, PET can distinguish reversible ischemia from irreversible infarction, which aids in selecting patients for medical or surgical treatment," they write. The level of oxygen metabolism in an affected area can help physicians gauge the viability of the damaged tissues and assist in treatment decisions.

In his editorial, Chalmers notes that "the time to evaluate a new technology with precision is when it is first tried in humans for the purpose of determining clinical efficacy. When information from poorly controlled evaluations gets around, the demand from physicians and patients becomes irresistible, and it's then very difficult to do a proper study." As an example of what can happen when new technology is widely used before it's properly tested, Chalmers points to the time and money that he maintains was wasted performing magnetic resonance imaging on patients who did not benefit from the information obtained.

As for who should pay for the studies, Chalmers suggests third-party payers cover early use in unproven circumstances, provided the patient is entered in a proper study. Routine use of PET should not be paid for unless its efficacy for the disease in question has been established through well-designed research, he says. "The early research will be paid for many times over by the money saved by not having to pay for improper use," he concludes.

JAMA November 11, 1988

HIV FOLLOW-UP

Homosexual men infected with the human immunodeficiency virus seem to run a greater risk of developing AIDS after three years of suffering lymphadenopathy syndrome (LAS), a generalized swelling of the lymph glands, says a report in the *Journal of the American Medical Association*. The study, by Jonathan E. Kaplan, MD, and colleagues at the Centers for Disease Control, Atlanta, involves 75 such men followed since 1982 and 1983. As of Nov. 30, 1987, 22 had developed AIDS five to 69 months after the onset of LAS. The cumulative incidence of AIDS was significantly higher in the fourth through sixth years after onset of LAS than in the first through third years, "suggesting that the risk for AIDS increases after the third year of LAS and that many more study participants will eventually develop AIDS," the authors say. They also note that a sharp decline in T-helper cell count, which often heralds the diagnosis of AIDS, "appears to occur at different times after the onset of LAS in different persons."

JAMA November 11, 1988

MALE OSTEOPOROSIS RISK

The "Questions and Answers" section of the *Journal of the American Medical Association* reminds readers that osteoporosis, while much more common in women, does occur in men. C. Conrad Johnston, Jr., MD, of the Indiana University School of Medicine, Indianapolis, notes bone loss is part of the aging process, although men have a higher bone mass at maturity and don't experience the accelerated loss rate caused by menopause. Johnston writes in response to a question about how to treat a 65-year-old man with apparent primary osteoporosis who is concerned about bone loss despite adequate exercise and vitamin D and calcium intake. In such a case, Johnston says it is first necessary to confirm the presence of osteoporosis via bone mass measurements. If confirmed, he says, it is necessary to rule out secondary causes, such as endocrine problems. Alcohol abuse and smoking are also important risk factors. Having done that, "an adequate intake of calcium and vitamin D, along with adequate exercise, should be sufficient," he says.

JAMA November 11, 1988

CONTACT LENS CAUTION

Improper contact lens care, such as using "homemade" saline solution in the disinfection process, is a major factor in development of bacterial infections that can damage the cornea. A letter in November's *Archives of Ophthalmology* now offers another caution to lens wearers, describing a case of infection associated with an aerosol can of preservative-free lens care saline. The authors, Paul Riodan-Eva, MB, of London, and

colleagues, say their 23-year-old patient had been traveling and was storing the can of saline in a bag with wet wash cloths. The cap was often found to be off the can, they note. Traces of the microbe *Pseudomonas aeruginosa* were found in the patient's right eye, his right contact lens, the top of the can and its contents. Another can sample was uninfected. "Users of aerosol cans of preservative-free saline should be advised always to store the can with its cap on and away from moisture," the authors write.

INFECTION RISK RELATED TO WOUND CARE. NOT TIMING OF ANTIBIOTIC THERAPY

Infection is a potentially serious complication after an open fracture (where the bone breaks the skin). But report in November's *Archives of Surgery* suggests local wound care, not timing or duration of antibiotic therapy, is key to preventing infection in such cases. The study, by E. Patchen Dellinger, MD, of the Harborview Medical Center, Seattle, and colleagues, followed 240 patients with open fractures of the arm or leg for development of infection after surgery. The main infection risk factors were fracture grade (degree of soft-tissue injury involved); location of the fracture in the lower leg and whether the fracture was repaired through internal or external fixation. "We conclude that the most important actions by the surgeon to prevent infection involve local wound care. There was no relation between the timing of antibiotic administration or duration of antibiotic therapy and infection risk," the authors conclude.

ARTERIOGRAPHY AND ANGIOPLASTY IMMEDIATELY AFTER HEART ATTACK

Performing cardiac arteriography and angioplasty immediately after giving clot-dissolving drugs appears to provide heart attack patients no advantage over waiting up to 48 hours to perform these procedures—and may even be harmful, a study in the *Journal of the American Medical Association* says.

The study, conducted by the Thrombolysis in Myocardial Infarction (TIMI) Research Group, examined whether heart attack patients did better when these invasive procedures to assess and widen blocked coronary arteries were performed immediately rather than 18 to 48 hours later. Considerable controversy surrounds this question, write the authors, Eugene Braunwald, MD, of Harvard University School of Medicine, and colleagues in the TIMI Research Group.

Although early treatment with thrombolytic agents—clot-dissolving drugs—has been shown to reduce mortality after myocardial infarctions, many patients are left with critically narrowed coronary arteries that often become clogged again, the authors say. Coronary arteriography gauges the degree of occlusion of arteries that

supply the heart muscle with blood, and angioplasty is a commonly used procedure that uses an inflatable balloon to widen blood vessels narrowed by atherosclerotic plaque build-up.

These invasive procedures, which involve snaking a catheter through an artery to the heart, are not without risk to the patient. This study, part of a larger investigation to assess optimum thrombolytic therapy for heart attacks, was conducted to determine the best time to perform these procedures following thrombolytic therapy.

All study subjects received recombinant tissue plasminogen activator (r-tPA), a genetically engineered clot-dissolving drug, within four hours of onset of their heart attacks. Angioplasty was attempted in 141 of 195 patients randomly assigned to the group receiving immediate catheterization and percutaneous transluminal coronary angioplasty (PTCA), and in 107 of the 194 assigned to the 18-to-48-hour PTCA group.

The authors report immediate catheterization and angioplasty provided no benefit over delaying the procedures for 18 to 48 hours after the start of thrombolytic therapy. The strategy of immediate catheterization and angioplasty did not improve global ventricular function, based on measurements of the heart's ability to pump blood. It also seemed to be associated with a higher risk of adverse side effects—such as bleeding that required transfusions and the need for emergency coronary bypass surgery—compared to the strategy of delaying the procedures 18 to 48 hours.

Performing the procedures immediately also was associated with a higher complication rate than performing them after 18 to 48 hours (12.4 percent vs. 4 percent). "The percentage of patients who died within the first 21 days was not significantly different in the two PTCA groups (7.2 percent vs. 5.7 percent in the immediate vs. the 18-to-48 hour PTCA groups)," the authors report. "These results indicate that routine immediate angiography and PTCA are not required after administration of r-tPA to patients with acute myocardial infarction."

In an accompanying editorial, Melvin D. Cheitlin, MD, of the University of California, San Francisco, describes the evolution of treatment of patients with acute myocardial infarction, which he says "has taken us, within a brief period of less than 40 years, from impotent observation to aggressive invasive intervention designed to open suddenly occluded coronary arteries." He questions the wisdom of the modern "do something, don't just stand there" spirit, which he says has led many clinical cardiologists to "finesse(d) the proof that this approach will be better than medical management or even better than later elective angioplasty."

Although he raises some questions about apparent biases in the TIMI study, Cheitlin says its findings are consistent with two different studies that clearly found no benefit from immediate angioplasty. "Each time immediate catheterization any time of day or night has been advocated, properly designed control studies have shown no advantage to this disastrously complicated, manpower-consuming, and expensive strategy," he concludes.

STUDY: POOR BLOOD SUGAR CONTROL PREDICTS DIABETIC RETINOPATHY

Diabetic retinopathy, the major cause of blindness in diabetics, appears strongly related to poor control of blood sugar levels, concludes a study in the *Journal of the American Medical Association*.

Diabetic retinopathy leads to progressive vision loss caused by the detachment of the retina, the light-sensitive membrane at the back of the eye. Although some authorities advocate tight control of blood glucose levels to prevent or halt further vision loss, evidence for this recommendation has been equivocal, say the study's authors, Ronald Klein, MD, MPH, and colleagues at the University of Wisconsin Medical School, Madison.

Their study, which followed 1,878 diabetic patients for four years, is the first large population-based prospective study to examine the relationship between blood sugar control and the incidence and progression of retinopathy. Patients were tested periodically for the degree of glycosylated hemoglobin, a test that indicates how well a patient has been controlling his or her blood sugar level. After controlling for age, sex, duration of diabetes and degree of retinopathy at the start of the study, the authors found a strong relationship between the amount of glycosylated hemoglobin and the incidence and progression of retinopathy. "The consistency of the finding and the strength of the association suggest a causal relationship," they write, but add that a population-based cohort study such as theirs cannot directly establish causality.

The findings suggest even a modest improvement of blood sugar control "may reduce the incidence of proliferative retinopathy significantly," they say. "For example, the four-year risk of proliferative retinopathy for persons with glycosylated hemoglobin of 11 percent, as compared with 9 percent at the baseline examination, was estimated to be roughly double... If intervention on glycemia can, indeed, cause such a reduction, the savings would be considerable."

In an accompanying editorial, Michael P. Stern, MD, and Steven M. Haffner, MD, of the University of Texas Health Science Center, San Antonio, discuss the merits of a population-based prospective study and say this one provides persuasive evidence that the degree of blood sugar control is positively associated with the risk of retinopathy development and progression. "The fact that such basic information has been so long in coming is testimony to the inferiority of the cross-sectional or retrospective approach, which has thus far given equivocal results on this important issue," they write.

Another JAMA article reports the possible cause of and preventive treatment for diabetic neuropathy, nerve degeneration that impairs sensory function in many diabetics. The authors believe peripheral nervous system damage may result from an accumulation of water in nerve fibers of diabetics. This may cause the fibers to swell and compress surrounding blood capillaries, cutting off blood flow to the nerve cells. The authors, Richard H. Griffey, PhD, and colleagues at the

University of New Mexico School of Medicine, Albuquerque, believe the water accumulates because excessive glucose in the nerve cells is transformed by the enzyme aldose-reductase into polyol, which draws water into the cell.

The authors used magnetic resonance imaging to examine water content of nerve fibers in four groups of men. Eleven were normal controls; 11 were diabetics with no neurological symptoms; 11 were diabetics with neurological symptoms; and six were symptomatic diabetics treated with a drug that inhibits aldose-reductase enzyme activity. The authors found large amounts of water in nerve fibers in 54 percent of the untreated diabetics with neuropathy symptoms, but levels in symptomatic diabetics treated with aldose-reductase inhibitors were normal. They also found abnormal amounts in nerve fibers of two asymptomatic diabetics, which suggests nerve edema may be an early event in the development of diabetic neuropathy. The nerve water content of five patients with long-standing neuropathy was normal, suggesting established nerve damage may be irreversible despite a return of the nerve water level to normal, they write.

"The availability of aldose-reductase-inhibiting drugs that would block the accumulation of polyol and water makes this hypothesis of the origin of diabetic neuropathy scientifically testable and offers a potential approach to clinical therapy," the authors conclude.

JAMA November 18, 1988

DOES ANESTHESIA CONTRIBUTE TO SURGICAL MORTALITY?

Patient characteristics and surgical risk are more important determinants of surgical mortality than anesthesia practices, a study in the *Journal of the American Medical Association* indicates. The report, by Marsha M. Cohen, MSc, MD, MHSc, FRCPC, of the University of Manitoba, Winnipeg, and colleagues, used vital statistics data and follow-up information on 100,000 cases of anesthesia use to analyze deaths occurring within seven days of a particular operation. The mortality rate increased with advanced age, with a marked increase in those over age 80, and males had nearly twice the mortality rate of females. Physical status was "a powerful predictor" of postoperative mortality, the authors say, with the seriousness of the surgery another key risk factor. But duration of anesthesia and inhalation techniques were not associated with increased postoperative mortality. Nor was the experience of the anesthesiologist, although the authors stress that this finding "should not imply that the human factor or training of the anesthetist does not affect operative events." Still, they conclude, "with regard to overall surgical mortality, our study has found that patient-related and surgical-related risk factors were more important in predicting mortality than the anesthetic-related factors that we studied."

JAMA November 18, 1988

DEPRESSION IN DEMENTIA TIED TO SPECIFIC BRAIN AREAS

Major depression is often seen in patients with primary dementia, such as those with Alzheimer's disease. Now, a report in November's *Archives of Neurology* suggests this problem is associated with degeneration of two areas of the brain stem involved in producing key neurotransmitters. Authors George S. Zubenko, MD, PhD, of the Western Psychiatric Institute and Clinic, Pittsburgh, and John Moossy, MD,* of the University of Pittsburgh School of Medicine, studied brain tissue from 37 demented patients with and without depression, and from seven controls with no history of either problem. The depression patients had significantly more evidence of degeneration in two brain areas, the locus ceruleus and substantia nigra, than did demented patients who were not depressed. These parts of the brain produce norepinephrine, which is involved in mood and sleep cycles, and dopamine, which is involved in motor activities. The data "suggest that coexisting abnormalities of multiple neurotransmitter systems may be required for the typical syndrome of major depression," the authors say.

TUMOR NECROSIS FACTOR IN OTITIS MEDIA

Tumor necrosis factor (TNF), an important immune system mediator, may play a role in the development of chronic otitis media with effusion (OME), or fluid in the middle ear, the most common form of middle ear inflammation in children, says a study in November's *Archives of Otolaryngology-Head and Neck Surgery*. The authors, Dov Ophir, MD, of the Kaplan Hospital, Rehovot, Israel, and colleagues, studied middle ear fluid in 23 children aged 3 to 8 with chronic OME. They found evidence of TNF in about two-thirds of the samples studied. As for the other patients, the researchers say their disease may have been at a different stage or "TNF may not participate in all cases of OME." The stimuli that cause production of TNF in the middle ear have yet to be defined, they say, but "elucidation of the mediators that take part in immune reactions in the middle ear mucosa may lead to more specific therapeutic strategies in this disease."

RARE MALIGNANT MESOTHELIOMA IN CHILD

Malignant mesothelioma is an uncommon tumor usually seen in middle-aged men with a history of asbestos exposure. But a report in November's *Archives of Pathology and Laboratory Medicine* describes a rare case in which this tumor was seen in a child—even more unusual in that the patient, a 13-year-old girl, had malignant mesothelioma of the peritoneum, the lining of the abdominal/pelvic cavity. Authors Gordon R. Armstrong, BMedSci, BM, BS, and colleagues at the

Children's Hospital, Birmingham, England, note that the lung is the most common site for this disease in adults and the few reported cases in children. The cause of childhood cases is unclear, they say. "In childhood... malignant mesothelioma has been reported as early as 2 years of age, and although exposure to asbestos in early life may lead to an accelerated progression in actively growing tissue, several studies have failed to identify asbestos exposure in childhood cases."

REPORT CONFIRMS ZIDOVUDINE'S EFFECTIVENESS IN AIDS PATIENTS

A study in *Journal of the American Medical Association*, involving the largest and most diverse AIDS patient cohort yet evaluated, confirms that zidovudine (formerly AZT) greatly improves survival in AIDS patients, reporting 73 percent overall survival nearly a year after their start of therapy.

The study, by Terri Creagh-Kirk, MS, of the Burroughs Wellcome Co., Research Triangle Park, NC, and colleagues, involved 4,805 patients with previous bouts of *Pneumocystis carinii* pneumonia (PCP) given zidovudine under a Food and Drug Administration "compassionate" or Treatment Investigational New Drug program. The program ran from October 1986 through March 1987.

Overall survival at 44 weeks after start of therapy was 73 percent, 88 percent in patients with better clinical status prior to therapy. "Data from the current study imply that initiation of treatment early in the disease process after the diagnosis of AIDS materially affects prognosis," the authors say. "... the finding of a strong association between stage of illness at time of initiation of therapy and survival suggests the need for study in patients still earlier in the disease process." Patients with transfusion-acquired AIDS had a poorer prognosis than others, but this may be due to several factors, the authors say.

The latest survival estimate "is significantly above that described in previously reported natural history cohorts (AIDS patients not treated with zidovudine)," the authors say. However, they say, this comparison is offered "simply to provide a reference point," not to make a statistical comparison.

The authors report no data suggesting drug-related toxic effects not previously attributed to zidovudine. But they do note a number of possible study limitations, including potential inaccuracies in some data, possible underreporting of some patient deaths and incomplete follow-up. However, they say, extensive efforts were made "to achieve high-quality and complete data."

In an accompanying editorial, John A. Bartlett, MD, of the Duke University Medical Center, Durham, NC, acknowledges the study's shortcomings but says the report, due to the large amount of data it contains, still provides "important confirmatory evidence supporting the efficacy of zidovudine in patients with AIDS and ARC."

"Zidovudine has provided the important first step in

the emerging science of HIV therapeutics," he writes. "Contrary to early predictions of the limited lifetime of zidovudine, its future appears bright due to the paucity of alternative antiviral agents with similar efficacy and acceptable toxicity, and as studies to broaden the therapeutic indications for zidovudine continue."

In another editorial, Jere E. Goyan, PhD, of the University of California-San Francisco, congratulates the authors for extracting useful data from a research protocol with admitted shortcomings, but raises questions about whether zidovudine is a good example for future FDA regulation of drugs indicated for life-threatening diseases. Such questions "lead me to believe that our system need much more than adjustment of the present process."

"It is time for us to consider the bases on which the current process was developed," Goyan writes. "In particular, we need to consider alternative study designs that allow the patient maximum hope for cure and the opportunity for some control over his or her destiny."

In a related report, John C. Pottage, Jr., MD, of Rush-St. Luke's Medical Center, Chicago, and colleagues suggest zidovudine also may be useful in treating HIV-related thrombocytopenia, or decreased platelet count. The report describes three patients with thrombocytopenia given zidovudine after conventional therapy was discontinued. All three responded with a sustained increase in their platelet counts, which dropped when zidovudine therapy was discontinued.

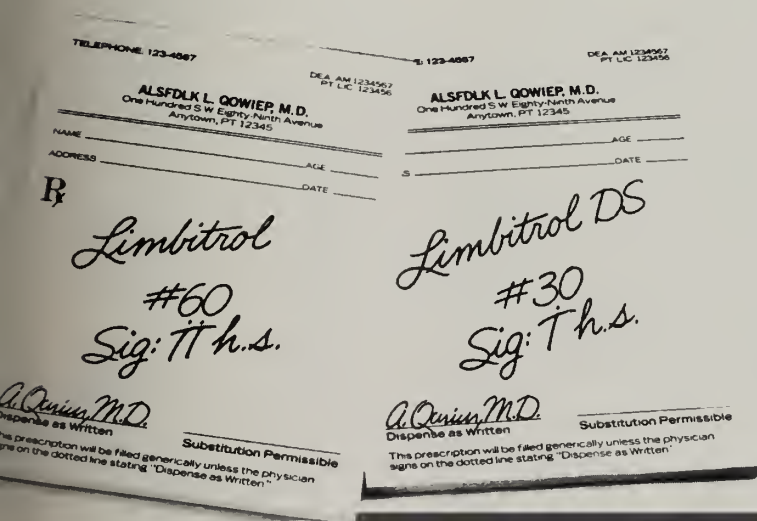
Although it is unknown whether zidovudine's antiviral effect caused the patients' platelet counts to increase, the authors say the improvement is not likely to have been a coincidence. "Further studies examining the prospective use of zidovudine in the treatment of HIV-related thrombocytopenia are indicated," they conclude.

JAMA November 18, 1988



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Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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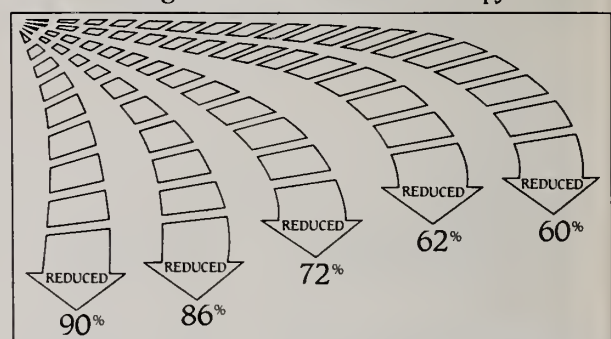
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Mammography
can detect
breast cancers
even smaller
than the hand
can feel.



Low-dose breast x-ray, mammography, is giving hope that the leading cause of cancer deaths in women will be greatly diminished.

We urge women without symptoms of breast cancer, ages 35 to 39, to have one mammogram for the record, women 40 to 49 to have a mammogram every 1 to 2 years, and women 50 and over, one a year. Breast self-examination is also an important health habit and should be practiced monthly. Ask your local Cancer Society for free leaflets on both subjects.

The American Cancer Society wants you to know.



Nuestra Portada

Cotorra Puertorriqueña. Obra de Rafael Rivera Rosa, artista natural de Comerío. Nació en 1942, pero su niñez transcurre en Nueva York donde estudia en "The School for Industrial Arts". Regresa a Puerto Rico en 1956; ingresa en el Taller de Artes Gráficas del Instituto de Cultura y estudia también en los talleres de la Galería Campeche.

El artista es considerado parte del grupo de pintores del país caracterizados por su dedicación a la pintura en afirmación de la puertorriqueñidad. Ha participado extensamente en exhibiciones individuales y colectivas en el Instituto de Cultura Puertorriqueña, Galería Colibrí y otras.

La obra que aparece en nuestra portada pertenece a la colección privada del doctor Radamés Sierra, Reumatólogo de San Juan. La Junta Editora agradece al autor y al doctor Sierra su colaboración para hacer posible la publicación de esta obra en nuestra portada.

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CLINICAL STUDIES

Determinants of Mortality in Patients with the Syndrome of Persistent Pulmonary Hypertension of the Newborn

Gloria Reyes Baez, MD
Carlos A. Pérez, MD
Francisco Vélez Reboyras, MD
Marta Valcarcel, MD
Rafael Zapata, MD

Persistent pulmonary hypertension of the newborn (PPHN) continues to be the most challenging syndrome seen in the Neonatal Intensive Care Unit (NICU). Despite current therapeutic modalities, the mortality continues to be high. Studies determining criteria to predict mortality vary from institution to institution. The purpose of this study is to identify the criteria associated with an increased mortality in infants admitted to the NICU of the University Pediatric Hospital in San Juan, Puerto Rico during a period of 15 months.

Materials and Method

During the period from February 1984 to May 1985, we identified 38 infants who developed the syndrome of PPHN from a total of 760 newborn infants admitted to the University Hospital Intensive Care Unit. This represented 5% of all admissions to the unit during this period. The diagnosis of PPHN was based on the following criteria: persistent hypoxia in an FI_{O2} 1.00, a preductal and postductal oxygen difference of more than 20mmHg, echocardiographic findings of right to left shunting through the foramen ovale, patent ductus arteriosus, or both, in the absence of structural heart disease and autopsy data. The majority of the newborn infants (75%) were transferred from other hospitals and admitted to the NICU with cyanosis and respiratory distress. The treatment of all these infants included mechanical ventilation with FI_{O2} 1.00, paralysis with Pancuronium, and correction of metabolic acidosis. Dopamine was used as needed to treat hypotension. Priscoline was tried in only three patients. All patients except three were hyperventilated. Hyperventilation was considered successful if the PCO₂ could be reduced to 25mmHg. In all patients the syndrome of PPHN was

secondary to a primary disease. Patients with primary or secondary pulmonary hypoplasia were not included in this study. The survival rate was 66%.

A retrospective analysis of the records of all infants with the diagnosis of PPHN was done. The patients were divided into two groups: survivors and nonsurvivors. Both groups were compared as to perinatal history, admission parameters and clinical course. The parameters chosen from the perinatal history included maternal age, gravity and perinatal complications among others. From the admission parameters we compared the arterial blood gasses, onset of symptoms and age at time of admission. The clinical course was evaluated comparing highest and lowest PO₂, PCO₂, PIP (peak inspiratory pressure) and Paw (mean airway pressure) and clinical complications. The results of treatment were also compared. The relationship of ventilatory parameters to the occurrence of air leaks was investigated comparing the highest Paw and PIP used in patients that developed air leaks and those who did not. The 2-tail student's T test for unpaired variables was used to compare both groups and when appropriate, Chi-square and Fischer exact test were used.

Results

There was no significant difference between the perinatal history of survivors and nonsurvivors (table 1). Both groups were comparable as to one and five minute scores, birth weight and gestational age. Admission parameters such as pO₂, pCO₂, pH, serum bicarbonate and mean blood pressure were not different between the two groups. Nonsurvivors had a later onset of symptoms than survivors (table 2). No relationship was found between the platelet count at admission and outcome. Although no difference as found in the mode of delivery of survivors and nonsurvivors, a high incidence (28%) of elective c-sections was observed in both groups of patients. The highest PIP and Paw were compared. Survivors required higher PIP and Paw than non survivors;

although, only the difference in PIP was significant. There was no difference in the highest AaDO₂ (alveolar-arterial oxygen difference) present in both study groups. Other parameters such as highest and lowest pO₂ and pCO₂ attained during the disease were also not different between the groups (table 3). The frequency of complications was compared. It was observed that overall, non-survivors had more complications (table 4). The complications which were more frequently observed in non survivors were sepsis, air leaks and intractable metabolic aci-

Table I

Perinatal History			
	Survivors	Non Survivors	
Maternal age	24±5	27±5	NS
Maternal gravity	2.25±1.4	1.8±0.8	NS
Maternal parity	3.2±2.4	2.6±2.2	NS
Apgar 1-min	6±1.9	6.5±1.9	NS
Apgar 5-min	6.5±2.1	6.5±1.9	NS
Birth weight	2814±469	2709±569	NS
Gestational age	37.8±2	37.8±2.6	NS

Table II

Admission Parameters			
Admission pCO ₂	±41.2±16	NS	
Admission pH	7.24±0.1	7.23±0.1	NS
Admission pO ₂	62.8±28.7	48.38±20	NS
Admission HCO ₃	16.1±3.6	16.8±7.2	NS
Admission BP (mean)	52.7±9.2	48.9±12	NS
Admission Age (Hrs)	12.8±9.3	13.5±13	NS
Onset Symptoms (Hrs)	1.42±1.3	3.5±4.2	P<0.05
Admission Calcium (Mg/dl)	7.3±2.1	7.9±2.4	NS

Table III

Clinical Course			
Highest pO ₂	173±0.79	170±89	NS
Lowest pO ₂	33.5±11.4	29.3±8.2	NS
Highest pCO ₂	53.1±12	52.6±1.3	NS
Lowest pCO ₂	21±7.6	18.6±3.8	NS
Highest PIP	43.3±9.5	51.6±8.3	P<0.05
Highest Paw	17.3±4.8	21.5±5.6	NS
Highest AaDO ₂	614±2.74	616±25.6	NS

Table IV

Complications			
Complications	Survivors	Non Survivors	
Pneumothorax	5	9	p<0.05
Other airleaks	2	9	p<0.05
Hypotension	6	8	NS
Sepsis	5	7	p<0.05
Intractable metabolic acidosis	1	5	NS
Heart failure	1	1	NS
Atelectasis	1	6	p<0.05
Total	21	45	p<0.05

dosis. The complications most significantly associated with mortality was the occurrence of air leaks. A relationship between the ventilatory parameters (highest PIP and highest Paw) and the occurrence of air leaks could not be demonstrated (Figure 1). No significant relationship was found between the highest AaDO₂ and the occurrence of air leaks. The relation of treatment to mortality was examined. The success of hyperventilation was determinant of outcome in our patients (Figure 2). A majority of the patients who survived required less than 72 hours of hyperventilation. There was a significantly higher mortality in patients with sepsis (Figure 3); although, no single organism was implicated. None of our patients responded to the use of Priscoline. The cause of death in most of our patients was septic shock or cardiogenic failure.

RELATION OF AIRLEAKS AND VENTILATORY PARAMETERS

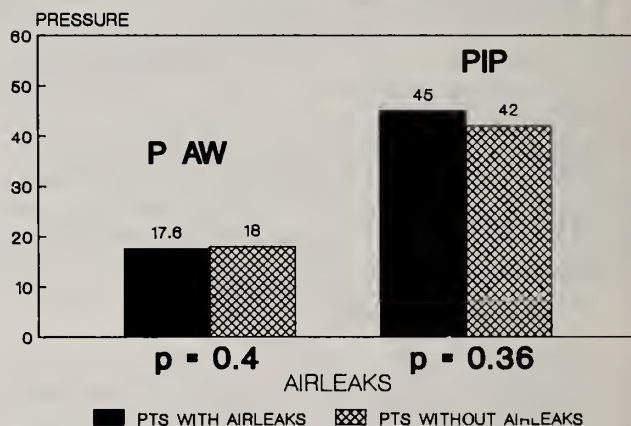


Figure 1

RESULTS OF HYPERVENTILATION

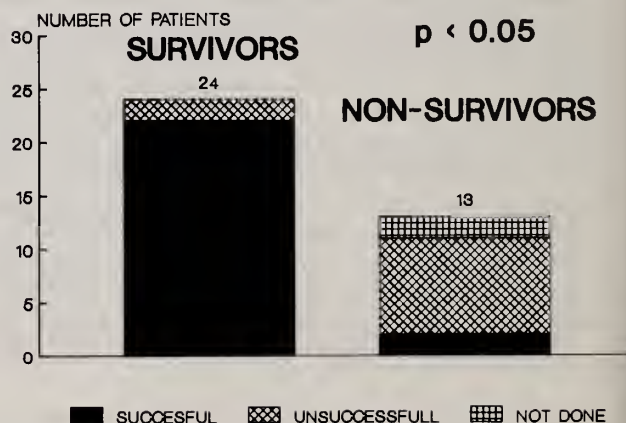


Figure 2

RELATION OF SEPSIS AND OUTCOME

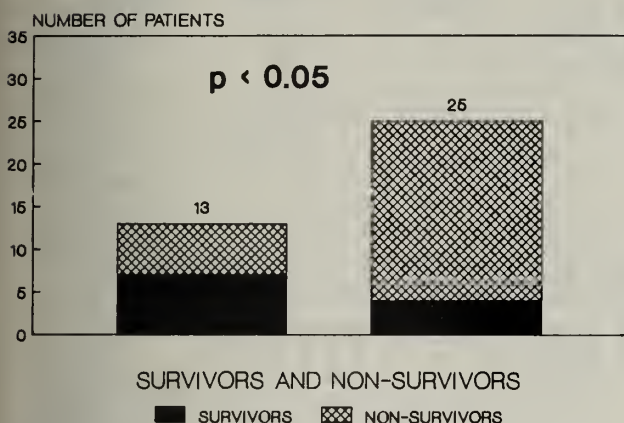


Figure 3

Discussion

Despite recent advances in the care of infants with PPHN, mortality rate continues to be high. Different institutions report mortality rates between 30 to 60%.^{1, 2} This difference in mortality may be due to the wide variety of associated clinical conditions and the severity of the illness. Most of the patients that die, do so within the first 2 to 5 days of life after a downhill course of progressive hypoxemia, hypotension and intractable acidosis.³ It is important to identify early in the course of the illness those infants who will not respond to maximal medical support, hyperventilation or vasodilator therapy so that new modalities of treatment such as extracorporeal membrane oxygenation (ECMO) or high-frequency ventilation (HFV) can be instituted. ECMO and HFV have been reported as an effective treatment in some of these critically ill infants.^{4, 5} These new modalities of treatment are not without risk and complications; despite results showing increased survival. ECMO has been associated with an increased incidence of cerebral infarction presumably from ligation of the common carotid artery and internal jugular vein.^{5, 6} HFV has been associated with significant necrotizing tracheobronchitis. Of interest is a recent report by Wung, et al. showing 100% survival without hyperventilation, paralysis, ECMO or HFV.⁷ The use of hyperventilation in all patients with PPHN has been questioned in another recent study. Duvoretz et al., showed that six patients that met the criteria for ECMO therapy did well with conservative management.⁸

The search for factors which may help identify patients at higher risk of mortality is difficult due to the presence of multiple factors that influence outcome. Nevertheless, some authors have observed a higher mortality in certain groups of patients. Patients with pulmonary hypoplasia, Group B streptococcus and patients who have suffered severe asphyxia have been observed to be at higher risk of mortality.⁹ Pulmonary hypertension in the presence of pulmonary disease appears to be associated with a higher

mortality than pulmonary hypertension in the absence of pulmonary disease.¹⁰ Drummond found that the results of arterial blood gas measurements in the first 72 hours had a prognostic value. She found a statistically significant difference in the highest and lowest pO₂ and pH during the first 72 hours of life. She suggested that the ultimate outcome of the disease was determined by the degree of hypoxemia secondary to the pulmonary hypoperfusion.³ We could not demonstrate this to be true in our patients. Others have suggested that the presence of pulmonary microthrombi reflected by a decrease in platelet count is associated with a higher mortality.¹¹ Peckham identified as prognostic factor the inability to decrease the pCO₂ with hyperventilation and the requirement of PIP higher than 35-40mmHg.⁹ Based on this, we would have expected a higher mortality in our patients since they all required more than 40mmH₂O of PIP. Higher mortalities have been seen in patients who develop left ventricular dysfunction associated with hypoxia, acidemia and pulmonary hypertension.¹² In adults the AaDO₂ difference has been advocated to identify patients with higher mortalities. Patients with AaDO₂ of over 620 mmHg for a sufficient period of time have a mortality of close to 100%.⁸ The average AaDO₂ of our patients was over 600 mmHg and of these 65% survived. Some of our patients who survived had AaDO₂ of more than 640mmHg at some time. This parameter does not seem to have the same implication in newborn infants as it does in adults and recently its usefulness in predicting survival has been questioned.¹³ Spitzer et al., have reported a scoring system that when performed within 24 hours of life, is highly predictive of outcome in infants with PPHN. This scoring system uses the maximal ventilatory frequency, the critical PCO₂, the maximal PIP, the lowest pH and the 5 minute apgar scores.¹⁰ In our patients,⁴ the lowest PCO₂, the maximal PIP and the 5 minute Apgar scores were not significantly different in survivors and nonsurvivors.

A significant finding in our patients was that the onset of symptoms was later in the patients that died. A probable explanation is that the symptoms were identified later and these patients were more ill at the time treatment was initiated. Most of our patients (75%) were transferred from other hospitals, mainly from hospital without neonatal care facilities.

The high incidence of elective c-sections (10/38) among the infants who developed PPHN deserves attention. Many of these babies were borderline prematures in which no studies had been done to confirm the gestational age. The association of elective c-section with perinatal asphyxia has long been recognized.^{14, 15, 16}

Hyperventilation was advocated as a treatment for this disease by Fox in 1983.^{1, 17} This mode of ventilation is associated with a high incidence of barotrauma and complications. Ventilation of poorly compliant lungs is associated with an increase in the incidence of air leaks. Since this was the factor which determined mortality in our patients we attempted to relate it to the ventilatory parameters. We could find no relation of ventilatory parameters and the high incidence of air leaks. This was also observed by Mandansky in patients with RDS. He could not find any relationship between the maximal ins-

piratory pressures and the development of air leaks.¹⁹ Hyperventilation of poorly compliant lungs is associated with barotrauma. The absence of true alveoli in the newborn infant and the decrease in pulmonary surfactant observed in newborn with PPHN make these babies more susceptible to the development of air leaks.^{18, 20} The presence of infection, which was a factor that significantly affected survival in our patients, may have been a factor predisposing to air leaks. Hyperventilation may be very useful in some cases but does not appear to be treatment, *sine qua non*, for all cases with PPHN. Recent findings have called attention to the presence of electroencephalographic abnormalities in newborn infants undergoing hyperventilation.^{17, 20} Poorer neurodevelopmental outcome has been found in infants who have undergone extended periods of hyperventilation.^{21, 22} Better outcomes may be obtained with the judicious use of hyperventilation and close attention to the maintenance of the cardiopulmonary hemodynamics using volume expanders, correction of acidosis and avoiding barotrauma.

Future studies are needed to clarify the many unanswered questions. Collaborative studies are urgently needed to enlist greater number of patients from which more meaningful conclusions can be drawn. Early identification of patients at risk of developing PPHN is necessary to permit early transfer to specialized centers where appropriate evaluation of current and experimental therapies can be done.

Resumen: El síndrome de hipertensión pulmonar persistente del recién nacido (HPPR) es una de las principales causas de muerte en recién nacidos. Los factores que determinaron mayor riesgo de mortalidad en infantes recién nacidos con HPPR fueron investigados en 38 pacientes admitidos a la Unidad de Intensivo Neonatal del Hospital Universitario Pediátrico durante un período de 15 meses. Se compraron factores del historial perinatal, parámetros de la admisión, curso clínico, complicaciones surgidas durante la enfermedad y respuesta a tratamiento entre los que sobrevivieron y los que murieron.

La diferencia más significativa entre ambos grupos fue la mayor incidencia de complicaciones, especialmente de escapes de aire del pulmón ("air leaks") en los pacientes que murieron. Esta complicación no se encontró relacionada con los parámetros de ventilación. La respuesta al uso de hiperventilación (tratamiento usado en todos los pacientes) fue un determinante del resultado final. El uso de hiperventilación está asociado a una incidencia alta de neumotorax y de disturbios en el sistema nervioso central.

Existen otras modalidades de tratamiento que se están ensayando en pacientes con pobre pronóstico. Tanto el uso de ventilación de alta frecuencia como el uso de oxigenación extracorpórea están asociadas a complicaciones serias. Se hace necesario poder identificar temprano en la enfermedad cuáles son los pacientes con altas probabilidades de morir para poder escoger juiciosamente el tratamiento que se ha de instaurar.

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CASE REPORTS

Splenic Cyst: A Case Report

Raúl H. Márquez-Sarraga, MD
Marino Blasini, MD, FACS
Edwin González, MD

Abstract: The following presentation deals with a case report of a large true splenic cyst. After a thorough research of the available medical literature this appears to be the largest reported specimen of this entity.

In a common surgical practice splenic cysts are a rare entity; we recently performed an exploratory laparotomy on a young adult female patient with this finding. To our surprise after a thorough literature search it appears that this is the largest splenic cyst reported to date. It is our intention to present our case, discuss the etiology, diagnosis and findings.

Case Report

A 23 year old GOPO AbO female with no known history of systemic illness came to our service because of a mass in her upper abdomen for two years. She referred that the mass started as a sensation of fullness in the left upper quadrant and epigastric area, and that subsequently she was able to palpate a hard mass in this area. She reported that her abdominal girth had increased considerably over the past two to three months. The patient gave no history of epigastric pain, heartburn, or of early satiety. In addition, she had no history of trauma to her thoracic or abdominal areas. No history of recent weight loss, nausea, vomiting, anorexia, or fever was given. Her family medical history was unremarkable.

The physical exam showed a well developed, well nourished, afebrile, young female patient with no evidence of respiratory distress, who on abdominal exam presented with a large, fixed mass in the left upper quadrant and epigastric areas which was hard to palpation. Bowel sounds were present and there was no tenderness to palpation. The remainder of the physical exam was within normal limits.

A diagnostic workup was started with an upper gastrointestinal contrast study with barium which showed deviation of the stomach to the right upper quadrant and epigastric areas. An abdominal CT scan was then carried

out (see Figures 1 and 2) revealing a large cystic mass in the upper abdomen which was displacing the bowel in a caudal fashion, and which appeared to be of hepatic origin. An abdominal sonogram showed a large cystic mass with a solid component in which the spleen was partially identified. An upper gastrointestinal tract endoscopy revealed a normal esophagus, and a greater than normal size of the stomach with normal mucosa and peristalsis. The duodenal bulb appeared normal, but further advance of the instrument was impossible due to extrinsic compression of the second portion of the duodenum.

A routine laboratory workup including CBC, urinalysis, and serum chemistry was within normal limits.

With the above findings an exploratory laparotomy was performed via a transverse abdominal incision (see Figure 3) revealing a large complex vascular mass. This mass was found to be in continuity with the spleen and



Figure 1. CT scan of the abdomen (scout film) revealing a mass in the abdomen.

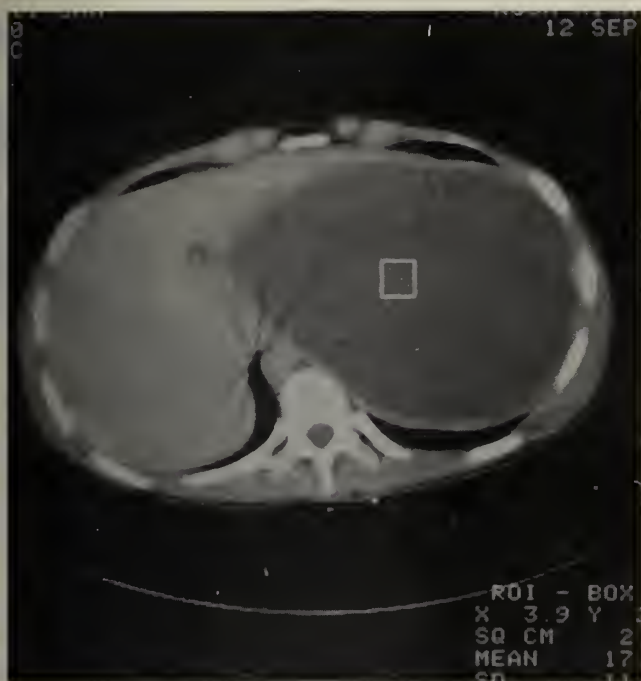


Figure 2. CT scan of the abdomen (transverse section) revealing a large cystic lesion which was thought to be of hepatic origin.



Figure 3. Intraoperative view showing transverse abdominal incision with a protruding mass (patient's head is to the right).

the splenic vessels were rotated anteriorly. After division of the splenic pedicle, and of an unusually large and strong lienorenal ligament, the mass was easily extracted. Closure of the abdominal cavity was performed in layers in routine fashion and no drains were left in place.

The specimen removed measured 26 x 19 x 15 cm, and had a weight of approximately 5,150 grams (11.3 lbs). The cystic component contained approximately 5,000 cc of a bloody fluid, and microscopic pathological examination showed a cyst lining composed of a low cuboidal, serosal type of epithelium.

The patient had an uneventful post-operative period, and she was discharged home without complications.



Figure 4. Splenic cyst (operative specimen) measuring 26 x 19 x 15 cm with a weight of 5,150 gm (11.3 lbs).

Discussion

The first splenic cysts reported in the medical literature were by Andral in 1829. In 1867, Pean performed the first splenectomy for a splenic cyst; and Grede in 1881 performed the first known splenectomy due to a post-traumatic splenic cyst. Later on, in 1953 Fowler^{1, 2} reported 265 cases as parasitic cysts and classified them. Martin³ in 1958 presented a new classification for splenic cysts which was later modified by Quereschi and Hatner in 1965. Over a 25 year period after reviewing 42,000 autopsies, Robbins⁴ was only able to identify 32 splenic cysts.

Actually they are classified as primary (or true) cysts, and secondary (or false) cysts (see Table 1).

Splenic cysts are rare; the parasitic variety which is more frequent in most areas of the world excluding the United States are more frequently caused by the *Echinococcus* variety of organisms. The non-parasitic cysts are then divided into true of false cysts depending on the presence of an epithelial lining of squamous cells (true cysts), and on whether there was antecedent trauma or hemorrhage (false cysts). Of these two varieties, the false

Table 1

Current classification of splenic cysts	
I. Primary (true) cysts: with epithelial lining:	
A. Parasitic	
B. Non-parasitic	
1. Congenital	
2. Neoplastic	
II. Secondary (false) cysts: without cellular lining	

cysts are more frequent than their epithelium-lined counterpart.

It has been postulated that epidermal cysts are caused by squamous metaplasia of mesothelial inclusions, but at the present time their etiology is still unclear. The epidermal lining of these cysts may also contain mucous glands.

An even rarer entity also found in the spleen are dermoid cysts which may contain sebaceous glands and hair follicles in addition to an epidermoid lining, and again, these are exceedingly rare.

The current treatment of choice is a splenectomy which entails meticulous surgical technique in order to avoid rupture of the cyst, as well as damage to the pancreas, left kidney, stomach, and splenic flexure of the colon. Drainage of the splenic fossa is not routinely performed unless damage to the pancreas or colon has resulted during mobilization of the spleen. In these patients it is particularly important to start aggressive respiratory therapy early in the post-operative period in order to avoid left lower lobe atelectasis which is the most common postoperative complication.

After a thorough review of the medical literature on this subject we have to state that this appears to be the largest true splenic cyst ever reported, since the largest one to date was reported by Pepicello⁵ in 1985, measuring 21 x 18 x 18 cm.

One of the purposes in reporting this case is to make the reader aware that splenomegaly has multiple etiologies, ranging from Hodgkin's disease, to the aforementioned cysts, and to the even rarer splenic tumors.

A discussion of the differential diagnosis of splenomegaly which is the usual presentation for a splenic cyst is lengthy and beyond the scope of this report. Nevertheless, we must remember that splenomegaly can be the result of a myriad of disease processes the most common of which are those secondary to acute or subacute bacterial, viral and parasitic infections. The reason for the splenic enlargement here is thought to be by a proliferation of antibody-forming cells.

In general, tumors of the spleen are rare and benign varieties may include hamartomas, lymphangiomias and hemangiomias. Primary and malignant tumors of the spleen are sarcomatous; the most common primary malignant neoplasm being angiosarcomas. Primary splenic lymphomas have been reported, but in these cases systemic lymphoma must be ruled out first.

The spleen is the most frequently injured organ following blunt trauma to the abdomen which is most frequently caused by automobile accidents. Some cases can present with "occult" splenic rupture which is a term applied to traumatic pseudocysts of the spleen when injury to the organ previously has not been diagnosed. Some of these may present with splenomegaly and have been treated with splenectomy when large enough due to the danger of rupture with intrabdominal exsanguination. This delayed rupture can occur with an interval of days or weeks after the traumatic episode.

We hope this paper will aid others in the diagnosis of unusual splenic pathology.

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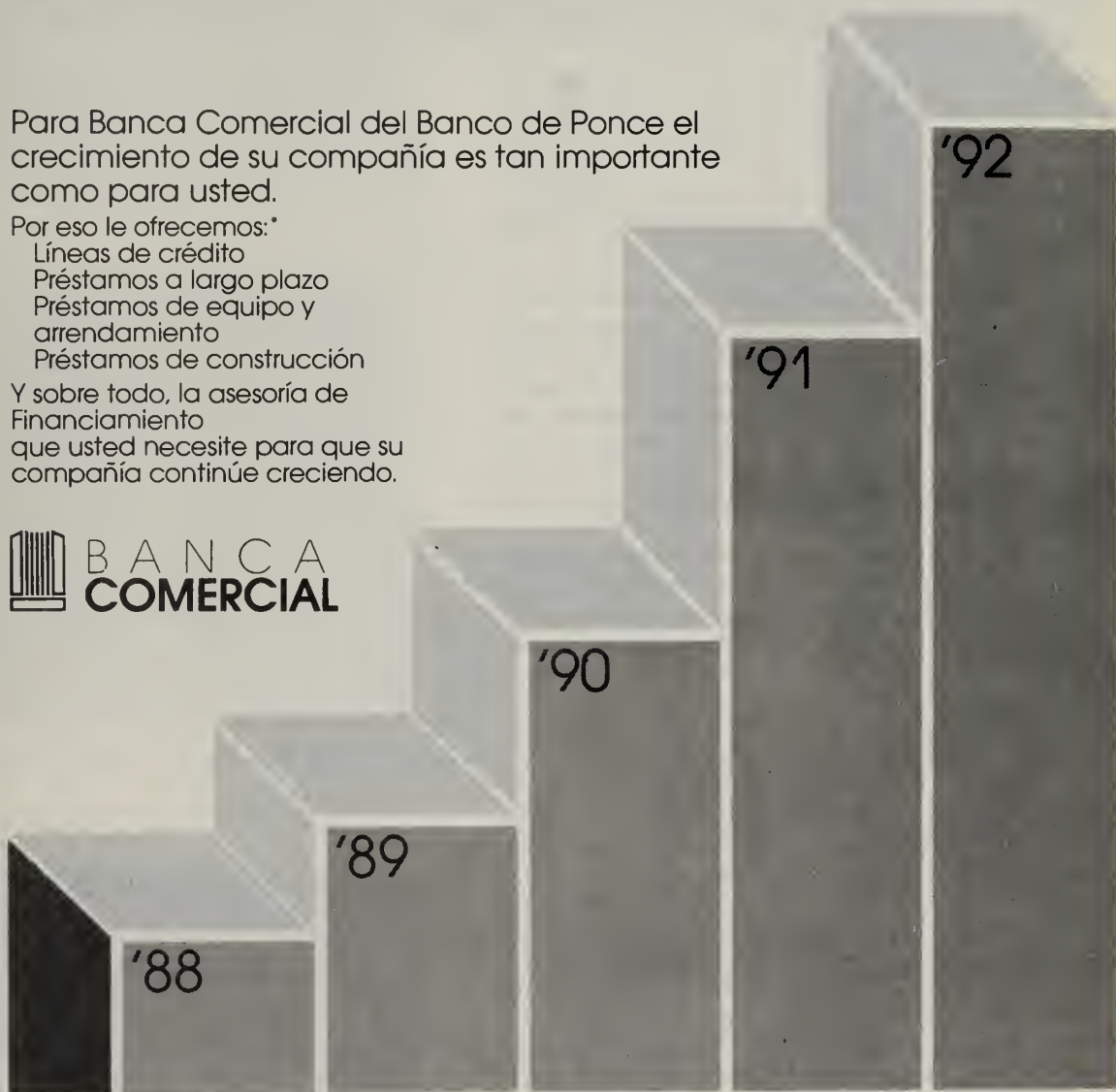
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Metástasis Osea de un Meningioma Angioblástico Intracraneal: Informe de un Caso

Román Vélez, MD
Vicente Torres, MD
Consuelo Climent, MD
Germán Lasala, MD

Resumen: Se reporta un caso de metástasis ósea múltiples de un meningioma angioblástico (hemangiopericitoma intracraneal). Desde el punto de vista clínico y patológico, es esencial tener presente que la variante angioblástica del meningioma tiene un mayor índice de recurrencia y metástasis que las otras formas de meningioma.

Los meningiomas se consideran tumores benignos del sistema nervioso central, que se originan de elementos celulares de las meninges y sus derivados. De los diferentes tipos histológicos de meningiomas, el angioblástico (hemangiopericitoma) tiene un comportamiento biológico diferente, ya que recurre con mayor frecuencia y en un período de tiempo más corto. Además, tienen una tendencia mayor a metastatizar y las metástasis extracraneales a hueso no son comunes.

Estamos informando un caso de meningioma angioblástico (hemangiopericitoma) con 4 recurrencias intracraneales y múltiples metástasis óseas extracraneales. Estas metástasis óseas no son usuales en este tipo de tumor.

Historial clínico

Paciente varón de 20 años de edad ingresado en el hospital por una masa dolorosa en el costado derecho. El paciente tenía un historial de meningioma angioblástico en la región parietal izquierda diagnosticado en 1983, por lo cual había sido intervenido quirúrgicamente 4 veces, debido a recurrencia del tumor. En la última recurrencia, además de la extirpación quirúrgica, recibió radioterapia y tratamiento profiláctico con difenilhidantoina para evitar convulsiones. Varias tomografías computarizadas posteriores no demostraron recurrencia del tumor.

Varios meses antes de esta admisión presentó dolor en la pierna derecha, que respondió a tratamiento con analgésicos. Un mes antes de la admisión presentó dolor en el costado derecho, de intensidad moderada a severa; el dolor no irradiaba, aumentaba con los movimientos y se aliviaba con analgésicos. El área afectada estaba hinchada y dolorosa a la palpación. El examen físico fue negativo excepto por una masa palpable y dolorosa en el reborde costal derecho.

Una radiografía de torax reveló múltiples lesiones líticas en ambas escápulas, clavículas, húmeros y la décima costilla derecha. Estudios radiológicos adicionales demostraron otras lesiones líticas en cráneo, vértebras (T₁₂, L₂ y L₄) pelvis y ambos fémures. También se pudo observar la presencia de una fractura patológica a nivel de la metáfisis proximal del húmero derecho. Una tomografía computarizada de la cabeza era compatible con recurrencia del tumor.

Los datos más relevantes obtenidos por los resultados de laboratorio al momento de la admisión fueron: calcio 11.1 mg/dl (N=8.5-10.5 mg/dl) albúmina 3.6 gr/dl (N+3.5 5 gr/dl) y fosfatasa alcalina 124 U/L (N=35-115 U/L).

Los diagnósticos a excluirse en este paciente fueron: un mieloma múltiple no secretor, hiperparatiroidismo, enfermedad metabólica ósea y carcinoma metastático.

Un aspirado de médula ósea sugería el diagnóstico de linfoma. Una biopsia de médula ósea fue compatible como tumor maligno metastático. En vista de la dificultad que existía para llegar al diagnóstico, se le practicó una biopsia de la lesión del húmero derecho.

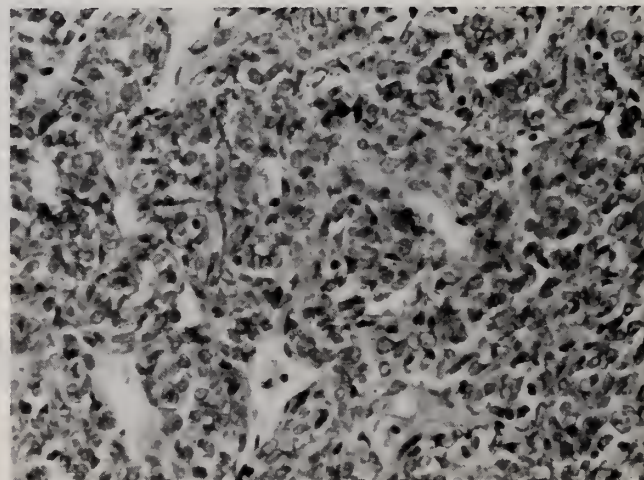


Figura 1. Metástasis de hemangiopericitoma meníngeo al húmero derecho. Grupos y cordones de células fusiformes parcialmente separadas por vasos sanguíneos. Células endoteliales aplanadas tapizan los vasos ramificantes. (Hematoxilina-eosina; 400X)

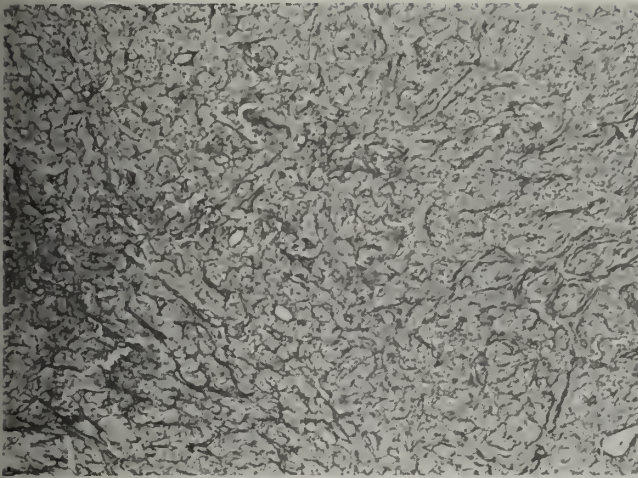


Figura 2. Hemangiopericitoma meníngeo. Tinte de plata que tiñe la reticulina de la membrana basal de los vasos sanguíneos y rodea a grupos de células neoplásicas. (100X)

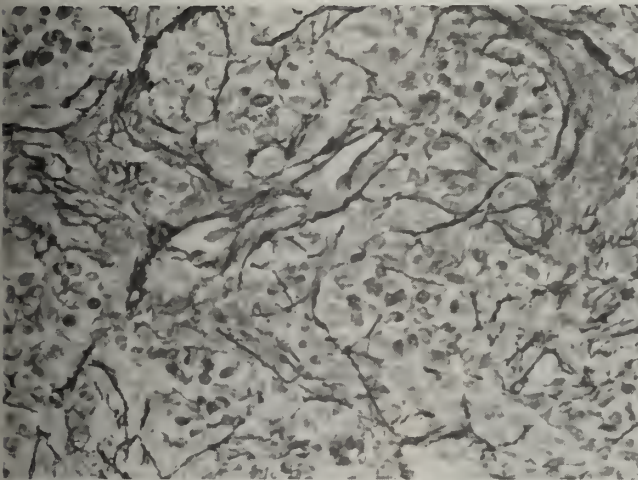


Figura 3. Hemangiopericitoma meníngeo. Tinte de plata. (400X)

Descripción Patológica

La biopsia del húmero consistía de múltiples fragmentos pequeños de tejido blando. Microscópicamente el tejido estaba formado por células tumorales, alargadas u ovals, con núcleos redondos en ovals. Las células tenían una disposición compacta, en forma de sábana, con numerosos vasos sanguíneos revertidos por una sola capa de células endoteliales. Se podían ver 3-4 mitosis por cada campo de magnificación alta. Era frecuente ver áreas de necrosis y hemorragia. Un tinte de reticulina demostró un patrón de crecimiento perivascular e intercelular.

La lesión se diagnosticó histológicamente como un hemangiopericitoma metastático. Al revisar la histología de las lesiones previas intracraneales, se encontró una histología similar.

Discusión

Los meningiomas son tumores que se originan de elementos celulares de las meninges y sus derivados, concretamente de las células meningoendoteliales arac-

noideas. Comprenden el 13-18% de los tumores primarios intracraneales y aparecen en cualquier edad, pero tumores de adultos principalmente, con una mayor incidencia a los 45 años. En la cavidad craneal son más frecuentes en mujeres (2:1)

El aspecto microscópico de los meningiomas es muy variable y usualmente estos tumores se dividen en subgrupos, de acuerdo a sus características histológicas (meningoteliomatosos, fibroblástico, transicional, psamomatoso, angioblástico y sarcomatoso). Estas distinciones no implican una citogénesis diferente para cada uno de los diferentes tipos histológicos. Por el contrario, se acepta que todas las variantes tienen su origen en el mismo tipo de célula y que la diversidad morfológica es una expresión del poder adaptativo de la célula de origen. Esto aplica a todos los tipos de meningiomas excepto el angioblástico.

El origen del meningioma angioblástico o hemangiopericitoma de las meninges es controversial, ya que algunos autores lo consideran como una variante del meningioma. Otros creen que es un tumor análogo al hemangiopericitoma de tejidos blandos, porque ambos tumores son indistinguibles histológicamente, y por tanto, esta variedad de tumor debe ser separado de la clasificación de meningioma, ya que tienen un comportamiento clínico diferente. Se han publicado numerosos estudios de microscopía electrónica, inmunohistoquímica y cultivos celulares, para tratar de definir el origen de este tipo de tumor, pero los resultados no han sido concluyentes.¹⁻⁸

La mayoría de los meningiomas clásicos son tumores benignos del sistema nervioso central. Sin embargo, el tipo angioblástico, desde su descripción por Bailey en 1928, se ha considerado un tipo de meningioma más agresivo.

Durante la cirugía, el aspecto del tumor es similar a los meningiomas benignos, pero en el meningioma angioblástico, es común una tendencia a sangrar abundantemente, requiriendo, muchos de ellos, transfusiones.^{9, 10}

En comparación con los otros tipos de meningiomas, este tumor presenta un tiempo de sobrevida postoperatorio más corto, con un índice de recurrencia mayor, así como una mayor incidencia de metástasis.¹¹ El tiempo promedio entre la operación inicial y la primera recurrencia ha sido reportado en 5 años^{9, 12} y las manifestaciones metastáticas ocurren, según series publicadas, entre los 7-8.6 años (promedio) después del diagnóstico de la lesión primaria.^{9, 11} Se han reportado metástasis en pulmón (más frecuente) tiroides, pleura, hígado, páncreas, riñón, adrenal, retroperitoneo, ganglios linfáticos, mama, mucosa bucal, mediastino y hueso.^{11, 12, 13} Este patrón de metástasis ha sugerido a algunos autores que el tumor se disemina por vía hematógena.¹² Las metástasis a hueso se consideran raras.^{12, 13}

En conclusión, la mayoría de los meningiomas tienen un comportamiento benigno, ya que aunque pueden infiltrar el cráneo, no infiltran el tejido nervioso y no metastatizan. El pronóstico depende de su localización y la accesibilidad para la cirugía. Sin embargo, el patrón angioblástico, hemangiopericitoma para algunos autores, debe separarse de las otras variantes de meningioma, porque su comportamiento es más agresivo, tiene una

mayor tendencia a recurrir, puede metastatizar y por tanto su pronóstico no es tan bueno.

Del estudio de este caso y de los casos publicados, se desprende que en todos aquellos pacientes con enfermedad metastática que tengan historial previo de hemangiopericitoma de meninges o meningioma angioblástico, se debe considerar al tumor cráneo espinal como posible tumor primario.

Summary: A case of multiple bone metastases from an angioblastic meningioma (intracranial hemangiopericytoma) is reported. From the clinical and pathologic point of view, it is essential to be aware that the hemangiopericytic variant of meningioma (angioblastic meningioma) displays a significant higher rate of recurrence and extracranial metastasis than other forms of meningioma.

Agradecimiento

Agradecemos la ayuda secretarial de la Sra. Luz M. López en la preparación de este manuscrito.

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SPECIAL ARTICLES

Medical Education in Puerto Rico: Proposals in Search of a Sponsor

José Ramírez Rivera, MD, FACP*

A year has passed since Dr. Vázquez Quintana published in this journal his thoughtful article about the *Regionalization of Medical Education in Puerto Rico*.¹ Neither the Council of Higher Education, nor the Department of Health, nor the Board of Medical Examiners seem to have considered his three most important suggestions: 1) that life be given to a Medical School of Mayagüez, 2) that a medical school sponsor the threatened residency programs in Ponce and Mayagüez, 3) that we stop accrediting substandard clerkships in unaccredited teaching facilities as internships (the insular internship, *internado jíbaro*).

I differ from Dr. Vázquez Quintana's implied suggestion that a proprietary (private) school be allowed to control and rule the teaching hospital farthest removed from the metropolitan area, a hospital at the top of the medical care ladder for 500,000 people in the Island's westside.

I think the University and the Government of Puerto Rico should reconsider the well-studied project of the 1970's to open a small medical school in Mayagüez. The excellent basic science and administrative structure of the western campus of the University are still there and the clinical facilities of the Mayagüez Medical Center have shown a will to remain nationally accredited.

This project was abandoned, even though it was clearly viable, when there was but a single smaller medical school in Puerto Rico. It was nurtured into inexistence by timidity and self-doubt, the now curious, and then unconsciously self-serving Río Piedran notion, that Puerto Rico could only afford one medical school. Records will show that, shortly before that time, the legislature paid a private corporation \$50,000 to study the feasibility of developing a medical school under the eegis of the University of Puerto Rico in Ponce. But the recommendation was not favorable: the only other campus with the scientific and administrative strength to add a medical science faculty was in Mayagüez.

Few people know, and Puerto Rican history will regret, that the possibility of federal support was explored successfully. A \$1.2 million subsidy was promised if the Government of Puerto Rico cared to establish a second medical school as recommended by the 1970 study of the Carnegie Foundation. University documents should indicate that a recently vacated science building at the Mayagüez campus (edificio Celis) could have been refurbished with all the trimmings to teach the first two years of the medical curriculum for half the subsidy; the sum estimated to make it fully functional was less than \$600,000.

A second way of drawing the strength of the University of Puerto Rico out of its metropolitan citadel was the Educational Consortium, an energizing educational tour the force which has received lauds from accreditation agencies nearly since its inception.² It intercommunicated and made necessary accredited postgraduate programs that serve three important health regions in Puerto Rico: Caguas, Ponce, and Mayagüez. It gave credence to the embryonic idea that perhaps the core of medical knowledge was more plentiful in regional institutions, that the elements of clinical medicine could be taught—and taught well—away from the rarified atmosphere of a supratertiary hospital in Río Piedras. The Educational Consortium opened widely a door of the medical school and its students to the needs and medical resources of the island of Puerto Rico. It led to teaching primary care in primary care environments in places as remote from the capital as Rincón.^{3, 4} It encouraged medical students from the University of Puerto Rico away from the medically overcrowded metropolis, to consider other places in the island to live and to practice.

The Educational Consortium of the Puerto Rico School of Medicine has given substantial support to the masterfully designed, functional, but withering concept of regionalization of health care.⁵ It is barely hanging on, rather than flourishing with an anemic budgetary allowance of \$750,000. The Department of Health—and perhaps the University—has been ready to profit from its success instead of encouraging its full development. The Consortium is a way to identify and attract well-qualified undergraduate and postgraduate teachers to medically

*Professor of Medicine, University of Puerto Rico School of Medicine. Director of the Western Branch of the Consortium of Medical Education of the University of Puerto Rico 1976-1982.

deprived areas of the island. It can be a bountiful source of medical talent for the identification of health problems and for the delivery of quality health care at the top of the regional health pyramid, the Regional Hospital. A special salary scale should have, but has failed to emerge for teacher-practitioners in the three Regional Teaching Hospitals under the Department of Health. No orderly identification of qualified teacher-practitioners has occurred. In its place alluring temporary contracts have been proffered to, at times, meagerly qualified groups of specialists transiently attracted to provide health care, but unable or not very willing to teach. In the meantime, the salaries of other teacher-practitioners in these *Regional Teaching Hospitals* have drifted, with each passing year, thousands of dollars further apart from the salaries of their equally educated brethren who eagerly choose to remain in the teaching hospitals of the metropolis. The patients of the island must come to them! A special salary scale for teacher-practitioners in Regional Teaching Hospitals could serve as a tangible encouragement for other regional hospitals to achieve Regional Teaching Hospitals status and thereby, hopefully, to be better conveyors of contemporary scientific medicine. An intelligent joining of conceptual goals and resources of the University and the Department of Health in their educational quest is needed, if we are to educate better physicians and to provide improved medical assistance for most of the population of the Island.

The subject of medical education should not be mentioned without being willing to look head-on at the unique, third-rate, insular pathway to the practice of medicine open to the marginally-trained physician. While the growing surplus of physicians encourages a sizable number of our more intelligent medical graduates to seek postgraduated training, and to consider establishing their practice in the mainland, it is a blatant anachronism that we continue to provide a structure "to have and to hold" foreign medical graduates unable to pass the necessary examinations to enter accredited programs.

It is reasonable and proper that large and medium size hospitals provide supervised clerkships to foreign medical graduates as a means of consolidation knowledge and developing clinical skills in preparation for a nationally (Puerto Rico and USA) accredited internship.⁶ But the hoax of dubbing as internship poorly supervised clerkships in hospitals who have no formal educational structure and are not accredited to teach should stop. The insular internship is fast producing an oversupply of mediocre practitioners which discourages the location of well-trained physicians in our towns. It promotes foreign medical graduates to arrest their professional growth at a level from which further development is very difficult. The insular internships guarantees serfdom to Puerto Rico forever. No one else recognizes it.

I would like to echo Dr. Vázquez Quintana's suggestions in this manner:

1. A medical school should open in Mayagüez (but sponsored by the University of Puerto Rico).
2. The three threatened residency programs in Caguas, Ponce and Mayagüez should intimately be associated with Liaison Committee accredited medical schools.
3. The Educational Consortium of Medical Education of the University of Puerto Rico and the Department of Health should join hands so as to provide salaries and fringe benefits appropriate to entice interested physicians in continuing a career as educators in the Regional Teaching Hospitals of Puerto Rico.
4. The accreditation as internships of clerkships in facilities not nationally accredited for medical education should be withdrawn.

Even those with limited foresight and narrow vision must see the light darkening at the end of the educational tunnel. A sponsor to correct our misguided trajectory in medical education is requested now.

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Bezafibrate in the treatment of hyperlipidemia*

P.Dieter Lang, MD

The European Atherosclerosis Society has recently adopted a policy statement entitled "The Recognition and Management of Hyperlipidaemia in Adults."¹ Major parts of this statement are devoted to the classification and the dietary and drug treatment of hyperlipidaemia. Five treatment groups are defined. Group A represents mild, group B moderate hypercholesterolaemia. Group C comprises subjects with hypertriglyceridaemia, group D those with elevation of both cholesterol and triglycerides. Finally, group E includes patients with severe hyperlipidaemia with cholesterol concentrations > 300 mg/dl and/or triglycerides > 500 mg/dl.

Diet is stressed as the first line of treatment. If response to diet is inadequate and the correction of a possible underlying cause of hyperlipidaemia fails to achieve specified lipid or lipoprotein concentrations, drug treatment is also required. Lipid or lipoprotein concentrations to be achieved by treatment depend on the presence of other marked or multiple coronary heart disease risk factors.

In the policy statement, the choice of drugs is delineated for each hyperlipidaemia group. Drugs suggested are anion exchange resins, nicotinic acid, fibrates and HMG-CoA-reductase inhibitors (when approved). Only nicotinic acid and the fibrates, singly or in combination with other drugs, are indicated in all five treatment groups.

A prominent member of the fibrate group is bezafibrate. It is administered at a dose of 200 mg t.i.d. or 400 mg o.d. in a sustained-release preparation.

Bezafibrate is rapidly and completely absorbed from the gastrointestinal tract. The drug is highly protein-bound. Its elimination half-life is approx. 2 hours. More than 95% of an administered bezafibrate dose is excreted with the urine, either as unchanged substance or in the form of metabolites. In patients with renal insufficiency, accumulation of the drug can be prevented by reduction of the administered dose.

Bezafibrate not only reduces the levels of the atherogenic lipids cholesterol (LDL) and triglycerides (VLDL) but also substantially increases the anti-atherogenic HDL. This makes bezafibrate an ideal drug for the treatment of dyslipoproteinaemias. There is mounting evidence from intervention trials that an increase in HDL cholesterol leads to a decrease in coronary heart disease incidence independent of reductions in total or LDL cholesterol. With bezafibrate, the HDL cholesterol

increase is most pronounced in patients with low baseline concentrations. In the majority of studies, the degree of HDL cholesterol increase was 10-30%. It may take several months until the maximum concentration is reached. Depending on the kind of hyperlipidaemia and the laboratory method chosen, increases may be found predominantly in the HDL₂ or in the HDL₂ subfraction. HDL apoproteins A-I and A-II also increase.

Clinical trials with bezafibrate so far have not been based on the new hyperlipidaemia classification of the European Atherosclerosis Society. Results derived from clinical trials in patients typed for hyperlipoproteinaemia or defined according to genetic criteria can be interpreted with regard to the new classification, however.

In hyperlipoproteinaemia type IIa or hypercholesterolaemia, bezafibrate reduces total cholesterol by approx. 20% and LDL cholesterol by approx. 25%. This reduction is accompanied by a decrease in apoprotein B. Changes in total and LDL cholesterol in patients with familial heterozygous hypercholesterolaemia were in the same order.²

In hyperlipoproteinaemia type IIb, cholesterol reductions are sometimes rather less prominent, but triglycerides or VLDL triglycerides are reduced by 40 or 50%. Excellent results with cholesterol reductions of approx. 25% and triglyceride reductions by more than 50% were seen in patients with familial combined hyperlipidaemia,² a frequent disorder found in patients with premature coronary heart disease. If a more extensive cholesterol lowering is required, bezafibrate can be effectively combined with lipid-lowering drugs having modes of action different from those of the fibrates.

Lipid abnormalities in hyperlipoproteinaemia type III, accompanied not only by premature coronary, but also peripheral atherosclerosis, can be corrected with bezafibrate.³

In type IV hyperlipoproteinaemia, triglyceride reductions are in the order of 40-50%. Reductions of approximately 60% can be achieved in hyperlipoproteinaemia type V. Bezafibrate does not only affect fasting but also postprandial triglycerides in hypertriglyceridaemia, thus reducing potentially atherogenic lipoproteins or their remnants for the major part of the day. In phenotypes IV and V hyperlipoproteinaemia, LDL is usually quite low. Below a concentration of 160 mg/dl, an increase in LDL cholesterol of approximately 10% may be observed. This, however, is accompanied by a compositional normalization of the LDL particle, making it more accessible to the physiological, non-atherogenic LDL receptor pathway.⁴

Bezafibrate is also effective in secondary hyperlipidaemia. This applies to patients with underlying renal

*Reprinted from *Heart Beat, the Journal of the International Society and Federation of Cardiology*, March 1988

insufficiency as well as diabetes mellitus. If the bezafibrate dose is adjusted according to the degree of renal impairment, lipids and lipoproteins can be safely and effectively modified. In addition to effects on lipids and lipoproteins as described in nondiabetic hyperlipidaemics, improvement of glucose tolerance is a unique feature of bezafibrate⁵ in diabetes mellitus. So far, hypoglycaemia has not been observed.

The lipid and lipoprotein changes induced by bezafibrate are maintained during prolonged administration, as shown in studies up to 4¹/₂ years.

Bezafibrate, administered in a dose of 400 mg once daily in a sustained-release preparations, has been demonstrated to be as effective as the standard dose of 200 mg t.i.d. The single daily dose can be administered either in the morning or at night with essentially identical results.

Apart from its effects on lipids, bezafibrate beneficially affects platelet function and blood viscosity. It also lowers fibrinogen, which was recently discovered to be a major coronary risk factor.

The modes of action of bezafibrate consist of inhibition of cholesterol and triglyceride synthesis, as shown in animal experiments. The former is due to inhibition of the rate-limiting enzyme of cholesterol synthesis, HMG-CoA-reductase. In man, catabolism of triglyceride-rich lipoproteins is increased by activation of lipoprotein lipase and hepatic triglyceride hydrolase. Catabolism of LDL is augmented due to promotion of the physiological LDL receptor pathway.⁶

Long-term studies of the effect of bezafibrate on parameters of coronary heart disease are under way.

Bezafibrate is well tolerated. The most frequently observed side effects are gastrointestinal symptoms which occur early after initiation of treatment, are generally transient and do not necessitate withdrawal of the drug. In rare instances allergic reactions, hair loss, and loss of libido have been observed. Rhabdomyolysis with CK increases are mostly seen when the dose is not adequately reduced in patients with renal impairment. Lithogenicity of bile increases slightly. It remains to be shown in long-term trials whether the incidence of gallstones increases.

When bezafibrate is administered to patients on oral anticoagulants, the dose of the latter must be reduced by approx. 30%. Since bezafibrate is partly bound to anion exchange resins, combined treatment is best carried out with the once daily administration of the sustained-release preparation. The resin is then given twice daily with the other two meals.

In summary, bezafibrate at its recommended dosage of 200 mg t.i.d. or 400 mg o.d. in the form of a sustained-release preparation produces substantial reductions in cholesterol and triglyceride concentrations in hypercholesterolaemia and hypertriglyceridaemia. It also markedly raises HDL cholesterol. Bezafibrate is indicated in hyperlipoproteinaemia types IIa, IIb, III, IV and V according to the Policy Statement of the European Atherosclerosis Society. It is also effective in secondary hyperlipidaemia. In diabetic patients, some improvement of glucose tolerance can be expected in addition to effects on blood lipids. Bezafibrate is generally well tolerated.

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FE DE ERRATA

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico desea señalar un error en la impresión del artículo titulado "Prevalence of Upper Gastrointestinal Mucosal Abnormalities at a Rheumatology Clinic" publicado en el Boletín de la Asociación Médica de Puerto Rico 1988; 80:241-244. En la página 243, segundo párrafo de la columna derecha se omitió una línea y se sustituyó por una repetida. El párrafo debió leer como sigue.

"In our study the presence or absence of symptoms was independent of the type of drugs taken (NSAID's or NSAID's plus prednisone). In conclusion, most patients attending a Rheumatology Clinic who were on NSAID's or prednisone therapy longer than 3 months had positive endoscopic findings, mainly minimal mucosal changes."

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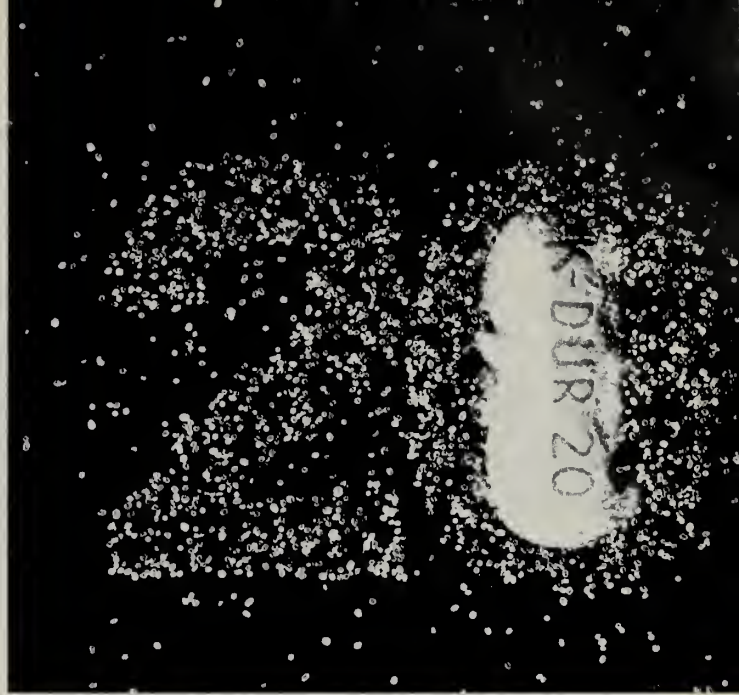
1. I think I have lumbago.
2. I'm type Z negative.
3. I'm on the grapefruit diet.
4. I gave six months ago.
5. I just got back from Monaco.
6. The lines are thirteen blocks long.
7. My mother won't let me.
8. I didn't sign up.
9. I'm going out of town.
10. Asthma runs in my family.
11. I forgot to eat this morning.
12. I'm allergic to flowering magnolia.



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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, AND OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS AND WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS AND WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

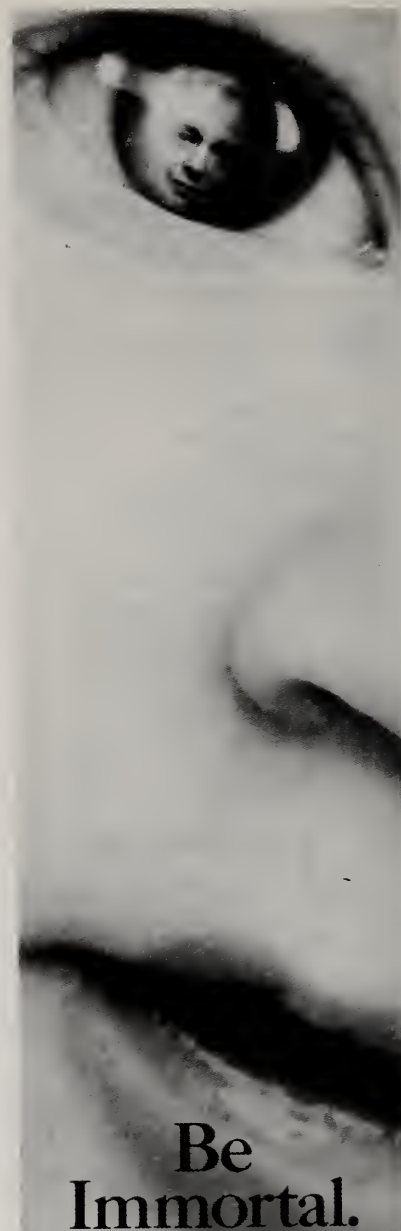
Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 mEq/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate.

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.



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Dilemas de la Práctica de la Medicina para el Siglo XXI

La Relación Médico-Paciente: Poder, Confianza y Sexualidad

Raúl Mayo Santana, Ph.D.

Esta conferencia trata sobre tres aspectos de la relación médico paciente: poder, confianza y sexualidad. Sobre la confianza en este tipo de relación se ha hablado mucho; en cuanto al poder y la sexualidad, muy poco.

Un sistema social

En un texto que utilizamos en la enseñanza de estudiantes de medicina,¹ se define la, relación médico-paciente como: un sistema social de dos personas que está determinado por las expectativas de los roles particulares de cada uno y por las personalidades individuales de los dos actores.² Se añade que el médico cumple dos funciones importantes que pueden facilitar u obstaculizar el tratamiento. Esto es, el médico provee apoyo emocional y legitima la enfermedad o el rol de enfermo del paciente. La relación en sí misma es considerada en este y otros textos como un factor terapéutico no-específico; el llamado efecto placebo, de carácter más o menos temporero, resultante del beneficio de recibir ayuda independientemente de su efectividad.

En su sentido más básico, la naturaleza social de esta relación está determinada porque existe, por un lado, una necesidad o carencia en la comunidad— de salud y enfermedad. Y por otro lado, porque existe un practicante que su trabajo y actividad consiste en ayudar y tratar la persona enferma. Practicante o médico clínico que es parte, hoy en día, de un complejo médico-industrial y un sistema de salud impregnado de éxitos, adelantos, frustraciones y conflictos. Sistemas que sus dimensiones actuales hacen pensar que la concepción de la relación médico-paciente como una interacción entre dos personas, o inclusive entre el médico y la persona y su familia, es una simplificación ridícula o una abstracción necesaria. Salpicada, por un lado, de romanticismo y, por otro lado, de aspectos todavía vigentes y reales de la relación que se resisten o sobreviven a los cambios.

La búsqueda de ayuda

El proceso de buscar ayuda, ante una necesidad (que implica una percepción, decisión y acción), es uno complejo que es materia de estudio. Para empezar, las personas pueden buscar ayuda no-médica antes o después de ir al médico— lo que puede retrasar o facilitar la decisión y acción. La auto-medicación o discusión de los síntomas con un farmacéutico, por ejemplo, es una ayuda *cuasi*-médica que dependiendo de las circunstancias puede desembocar en solicitar ayuda médica.

Las características de los síntomas asociados a este proceso de percepción de una necesidad de salud y decisión de buscar ayuda son: a) la frecuencia de los síntomas y la familiaridad con los mismos en la comunidad y, b) cuán predecibles y amenazantes pueden ser éstos para la persona.³

Los factores socioeconómicos son importantes. Por ejemplo, estudios realizados en Estados Unidos indican que las personas de las clases altas, por así decirlo, tienden más a reportarse enfermos que las personas de estratos bajos.³ La orientación hacia la enfermedad varía por clase social. Se ha encontrado que los sectores socioeconómicos bajos tienden a ser más "fatalistas" y están menos orientados a las medidas preventivas y a las consultas médicas.³ Factores económicos y educativos entran en juego no sólo en el proceso de buscar ayuda sino en el interior mismo de la relación médico-paciente, como ocurre en la comunicación y en el acatamiento del tratamiento o "compliance".

La edad y el sexo son aspectos demográficos que también establecen diferencias en los procesos de buscar ayuda. La tendencia de la mujer a solicitar más ayuda que los hombres es un hallazgo consistente. En Puerto Rico, donde las mujeres constituían en 1980 el cincuenta y un por ciento (51%) de la población, las mujeres realizan más visitas médicas al año que los hombres (4.6 y 3.6 respectivamente en 1981) y tienen una mayor incidencia de morbilidad o enfermedad aguda y crónica.⁴ En Puerto Rico, además, "entre las edades de seis a veinticuatro años hay una disminución en la utilización de los servicios de salud" y, luego, se observa una asociación positiva de mayor utilización a mayor edad.⁴

La percepción de enfermedad y la solicitud de ayuda

son sin lugar a dudas fenómenos socioculturales. El estrés psicosocial, las experiencias previas con la enfermedad y el sistema de salud, y las características personales de los individuos y las familias, se han identificado también como otros aspectos de importancia en la conducta de buscar ayuda. Los niveles de tolerancia al dolor y a la inconformidad y los niveles límites de ansiedad son factores culturales y personales que modifican esta conducta.³ De hecho, un síntoma en sí puede ser bastante tolerable, pero sus implicaciones pueden generar bastante ansiedad.

Los roles

El sociólogo estadounidense Talcott Parsons ha identificado cuatro componentes del rol social del enfermo: 1) se le exige de ciertas normas y responsabilidades; 2) no se le culpa, abiertamente, por su enfermedad ni se espera que se recupere por un acto de voluntad; 3) se espera que quiera mejorarse y salir del rol de enfermo; y 4) se espera que busque ayuda técnica competente y coopere en su tratamiento.^{2, 3, 5} Al igual que en el mundo laboral se dice que las uniones son los peores patrones, en el mundo de la salud se dice que los médicos son los peores pacientes. Paradójica, aunque quizás entendiblemente, les es muy difícil jugar el rol de enfermo y se sienten amenazados en el mismo.^{3, 6}

Parsons ha descrito también cinco aspectos claves del rol de médico. Se espera del médico, que: 1) tenga y mantenga un nivel alto de conocimiento y destrezas; 2) ayude y preste sus servicios sin discriminar; 3) practique aquellas áreas en las que es competente y utilice su conocimiento y destrezas con el propósito único de beneficiar al paciente y no para explotarlo o aprovecharse de él; 4) mantenga una neutralidad afectiva, que le permita ayudar en forma objetiva y que no mezcle el rol profesional y el trato humano con un involucramiento erótico-sexual o demasiado personal; y 5) tenga una orientación colectivista que le permita subordinar sus beneficios personales al beneficio del paciente de tal manera que facilite el desarrollo de la confianza.^{2, 3, 5}

Modelos de la relación

Se han identificado cuatro modelos que describen diferentes tipos de relación médico-paciente.² Los primeros dos, el modelo activo-pasivo y el modelo de consejero-cooperador, enfatizan un rol de dominación y control de parte del médico. El primer término en cada uno (activo-consejero) se refiere al médico y el segundo (pasivo-cooperador) al paciente. Ambos modelos tienen características asociadas con un rol de autoridad jerarquizado y con una actitud paternalista. El tercer modelo, de participación mutua, está basado en una relación más horizontal de respeto y colaboración mutua. Este modelo no niega el hecho de que la persona que solicita ayuda se encuentra, de entrada, en una posición de vulnerabilidad y dependencia. Sino que dentro de estas circunstancias se estimula y facilita el sentido de participación y autonomía. Finalmente, existe un modelo que, en general, es considerado como un modelo no funcional y en muchos casos no ético; pero que puede darse en la práctica como una desviación. Este es el modelo de intimidación social,

asociado más a una relación de amistad. Modelo que, como excepción, pueden practicar algunas personas en forma adecuada, pero por sus riesgos y posibilidades de explotación no es promovido y no se asocia con una conducta profesional.

El trabajo médico

Mencionamos anteriormente que la caracterización de la relación médico-paciente como un sistema social de dos personas determinado por los roles y personalidades de los actores es, por una parte, una abstracción necesaria, hecha aparentemente con fines de educación e investigación, y por otra parte, dado los cambios sociales ocurridos, corre el riesgo de ser una caricatura. Sucesos, tales como el desarrollo comercial-industrial del sector salud, la tendencia organizacional de realizar la práctica médica cada vez más en forma corporativa, la proliferación de diversas profesiones de la salud, y la fragmentación del servicio médico, entre otros, han llevado a una relación en que en uno de los polos, el médico, intervienen múltiples actores. Relación no sólo mediada por los factores mencionados de clase social, demografía y características personales, sino afectada también por intermediarios o agentes económicos que pagan y establecen límites a los servicios prestados. No tengo dudas que una tendencia de las sociedades capitalistas es hacia una mayor caracterización de la salud y la enfermedad como una mercancía.

Importante resulta ser también poder entender y estudiar la práctica médica como un proceso histórico y como un proceso de trabajo. Procesos en donde el ser humano enfermo o disfuncional corre el riesgo, como objeto y finalidad de ese trabajo, de terminar, como dijera el sociólogo Méndez Concalves, siendo "el cuerpo del paciente" o todavía más, "el cuerpo enfermo de el médico".¹⁰ Este fenómeno natural de objetivización y objetificación de todo proceso de trabajo tiene serias implicaciones cuando el objeto de trabajo es la salud de un ser humano.

El asunto de los instrumentos de trabajo —simbolizados en el término de la tecnología médica moderna— es uno que requiere mayor estudio. Especialmente en lo que concierne a su papel en la transformación de la relación médico-paciente y a las modificaciones que están ocurriendo en el seno de los contextos y las modalidades de la práctica médica. Por un lado, se afianza el aspecto técnico de la profesión, así como se amplía, además, las posibilidades y esferas de intervención. Tendencias ambas que fuerzan a un mayor énfasis en los aspectos humanísticos y éticos de la medicina, como contrapeso a los usos inadecuados de la tecnología.

El poder

Mucho de lo que he mencionado hasta ahora nos sirve en la consideración de los aspectos del poder, la confianza y la sexualidad. El médico ocupa en los tiempos modernos una posición socioeconómica de poder, autoridad e influencia. Los italianos dicen que la medicina "es aquella ciencia que dice al pobre cómo podría curarse si fuese rico".¹¹ En casi todas las épocas los médicos no solo han servido más a las clases ricas sino

que tienden en su práctica a reproducir las ideologías de las clases dominantes.¹⁰ Este rol ideológico explica en parte la separación que existía en la edad media (antes del Siglo XV) entre el médico y el cirujano, y la exclusión de la cirugía de las escuelas de medicina — particularmente en Inglaterra y Francia, no así en Italia.¹² Y van a ser precisamente la cirugía y la anatomía las que sienten las bases más firmes para el desarrollo científico de la medicina.¹²

Una noción general del poder¹³ relaciona al mismo con: a) la presencia de una interrelación vertical o jerarquía, principalmente en una sola dirección; b) con influencia o autoridad—sea esta basada en cualidades socialmente positivas o negativas —que emana de una posición social; y c) con niveles variados de coacción—donde el poder y el derecho jurídico convergen.

Hemos mencionado que una persona que solicita ayuda médica se encuentra usualmente en una posición más o menos vulnerable y dependiente. Esta situación ascribe a la relación médico-paciente cierto grado de desigualdad inicial. Si unimos a ésta los factores de rol, posición y clase social, y del poder que se puede ascribir también al control de la información y al dominio de una técnica y su terminología, podemos conceptualizar que en la relación médico-paciente el médico ostenta una posición de autoridad y dominancia. Aunque cualificada en muchos de sus aspectos en términos y por atributos positivos.

Esta desigualdad inicial y primaria se ha fundamentado, además, en un modelo todavía predominante en la medicina moderna, el llamado modelo biomédico.¹⁴ Modelo que falsamente ascribe a todas las enfermedades una causa biológica específica y se resiste a concederle importancia a la interrelación de factores biosociales. Esto es así, aun cuando sabemos que un conjunto grande de las llamadas enfermedades, en todas las áreas de la medicina, no tienen una etiología o causa conocida y solo pueden ser caracterizados como síndromes y desórdenes de estructura (anatomía patológica) y de función (patofisiología). En el mejor discurso médico se caracteriza a la enfermedad como la suma de fenómenos anormales mostrados por un grupo de organismos vivos en asociación a una característica o conjunto de características en común, por lo cual difieren de la norma de su especie en tal forma que los coloca en una desventaja biológica.¹⁵ Deberíamos añadir que “difieren de la norma funcional de su especie o grupo, en tal forma que los coloca en una desventaja biológica, social y psicológica.”

La medicina es una aplicación y práctica científica llena de incertidumbre. Aunque la medicina ha tenido un progreso enorme, todavía para el 1976 se conocían tratamientos efectivos o medidas preventivas en solo el 50-55% de las enfermedades más serias (unas 360).⁷ De ahí la importancia y reconocimiento que tiene lo de la “medicina como un arte y una ciencia” y del buen practicante como un “buen clínico”.

El pensamiento clínico tiene sus riesgos. Freidson¹⁶ identifica cuatro atributos claves del clínico, en contraposición a la mentalidad teórica-científica. El clínico tiende impulsivamente a la acción, a la intervención—de ahí en parte eso de que el remedio puede ser peor que la enfermedad. El clínico tiene que creer en lo que hace y así

proyectarlo; es un pragmatista consumado— está más interesado en resultados prácticos que en explicaciones teóricas; tiende a basar demasiado sus creencias y sus prácticas en su experiencia personal; y, a pesar de todo esto, reconoce la incertidumbre e indeterminación del trabajo médico.

Al mirar al interior del trabajo médico, la tradición todavía predominante de un modelo autoritario y paternalista acentúa la dominación del médico y explica en parte la insatisfacción existente con la medicina. La impotencia que siente el paciente y su percepción de que no se le trata como a un ser humano, es todavía más dramática en el contexto hospitalario. Como dijo un paciente informado a sus médicos en el hospital, luego de ser sometido a múltiples y constantes extracciones de sangre por órdenes de diferentes especialistas: “ustedes son todos buenos médicos, pero yo solo deseo un doctor”. Por cierto, escogió a una doctora graduada en el año 1940, ya que pensó que para una mujer haberse graduado en esa fecha tenía que haber sido el doble de buena que un médico varón.¹⁷

La confianza amenazada

La autoridad e influencia del médico, y su autonomía profesional (que es la mayor entre todos los profesionales), se ven amenazados hoy en día por el desarrollo industrial-comercial de la medicina. El médico asalariado que practica en organizaciones complejas donde predominan las formas corporativas y la ganancia como motor institucional dominante, es cada vez más la norma.^{7, 8, 9} La preocupación por los costos y la contención de los mismos ha ejercido efectos positivos y negativos. Los estudios realizados por propios médicos muestran consistentemente el gran número de procedimientos médicos innecesarios o inadecuados.¹⁸ Esto ha llevado a las asociaciones profesionales a trabajar intensamente en estándares y protocolos que garanticen una mayor calidad.^{19, 20}

En la parte negativa, para el rol y trabajo del médico, estos cambios inciden sobre un principio y aspecto esencial y básico de la relación médico-paciente: la confianza y el rol fiduciario (i.e., que depende del crédito y confianza que merezca) del médico, el rol como representante y defensor del paciente (“advocate”). Los aspectos de confianza, intimidación y confidencialidad son una parte esencial de la relación de ayuda y terapéutica médica.

La combinación del poder ostentado y concedido al terapeuta con la situación de un ambiente especial de dependencia, vulnerabilidad, confianza e intimidación tiene sus riesgos. Por sus riesgos y posibilidades explotativas es que el modelo de intimidación social en la relación médico-paciente es rechazado profesionalmente, aunque manifestado parcialmente en un sinnúmero de instancias prácticas.

El abuso sexual en la práctica clínica es un ejemplo de esta posibilidad y realidad. El paciente o médico seductor o el paciente o médico seducible²¹ conforman una realidad de la cual poco se habla. Y queda, la mayoría de las veces, enterrada culpablemente en el interior de la relación y de las personas.

El compromiso

No quiero terminar esta conferencia sin postular, aunque sea esquemáticamente, algunas alternativas y posibles soluciones. Primero, en cuanto a un modelo médico general, planteo la necesidad del desarrollo de una teoría ecológica de la medicina y de los procesos de salud y enfermedad. Las bases para el desarrollo de esta perspectiva ecológica, de interacción organismo-ambiente, se pueden encontrar tanto en los trabajos de Claude Bernard como de Louis Pasteur.¹⁴ Segundo, en relación a un modelo de relación médico-paciente, considero que el modelo de participación mutua, basado en una interacción de respeto, colaboración y responsabilidad mutua entre el médico y el paciente, es la alternativa que no solo promueve una relación más humana y de menos desigualdad, sino que mejor moviliza los recursos y las fortalezas existentes hacia una recuperación y un mantenimiento de la salud. Tercero, quiero apoyar la proposición de una práctica, aparentemente paradójica: más científica y con más compromiso humano, social y ambiental. Finalmente, contra la opresión latente en determinados aspectos de la relación médico-paciente: el profesional competente y consciente, el médico-educador, y el paciente informado. La conciencia y la educación aunque tienen sus límites pueden ser poderosas.

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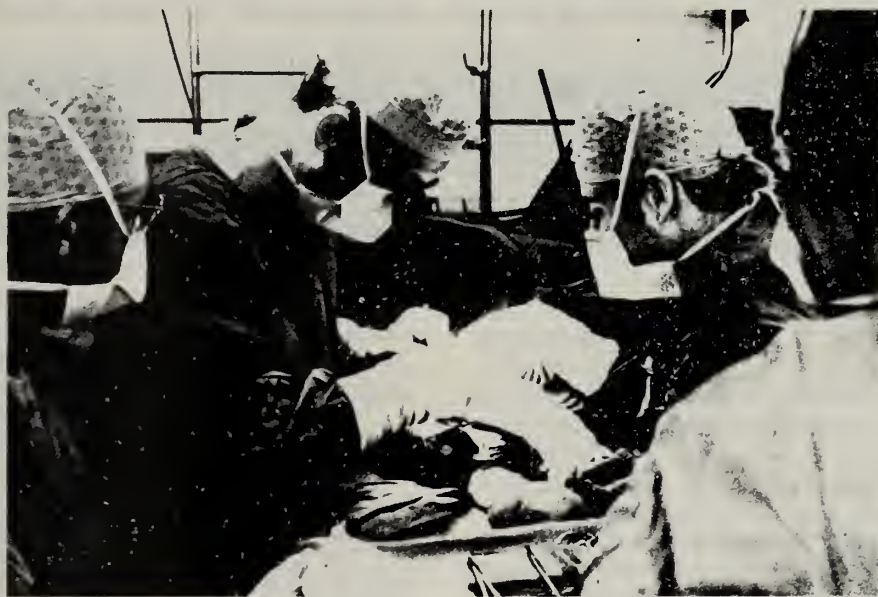
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MEDICAL ASPECTS OF NUTRITION

National Nutrition Objectives for the Years 1990 and 2000*

Marion Nestle, PhD, MPH*

For the past decade, the Department of Health and Human Services (DHHS) has led a major national effort to establish a public health agenda for the United States through development of measurable objectives for improved health status in priority areas of health promotion and disease prevention. The initial objectives were targeted for achievement by 1990. The process of developing objectives for the year 2000 is already well under way. This process requires commitment from individuals and groups in the federal, state, community and private sectors. Nutrition is designated as one of the key areas. Marginal success with the 1990 nutrition objectives mandates the need for nutrition professionals to be deeply involved in development and implementation of those for the year 2000.

National Health Goals

Recognizing that many prevalent causes of death and disability in the United States could be prevented or reduced through improvements in diet, exercise and other life-style practices, the Public Health Service (PHS) Act of 1976 authorized DHHS to establish national goals for disease prevention and health promotion and strategies to achieve them.¹ The first step was the publication of the 1979 *Surgeon General's Report* that called for increased attention to reduction of deaths and disabilities from preventable causes and that defined broad goals for health promotion among the various age groups to be achieved within 10 years.²

In an attempt to attain these goals, the report designated 15 priority areas for development of specific objectives in which the health-care system might be expected to have an impact.³ In recognition of the growing consensus on the relationship between diet and disease prevention as expressed by the 1979 *Surgeon*

*General's Report*² and by the *Dietary Guidelines for American*,² nutrition was designated as one of the key target areas for objectives development.

The 1990 Objectives

The 1979 report was followed in 1980 by a listing of 226 health objectives distributed among the fifteen target areas that were to be achieved by 1990.⁵ These objectives were developed through extensive consultation among a diverse group of experts who had been asked to identify the most important health problems in each area, to specify the most potentially effective intervention steps, to consider the availability of data on these issues, especially for high-risk groups, and to view the objectives as flexible guidelines rather than fixed obligations.³ Achievement of the objectives was expected to demand a commitment from local, state and federal governmental agencies and also from the private sector: industry, labor, voluntary health organizations, schools, churches, physicians, other health professionals and private citizens.⁶

National Nutrition Objectives

Engagement in this objectives-setting process represented the first attempt by the nutrition community to convert widely accepted priorities into precise, measurable goals.⁷ The results of this endeavor include the seventeen objectives listed in the Table. These objectives are designed to improve maternal and child health (objectives #1, 2, 8), to reduce dietary and diet-related risk factors for chronic disease (#3-7, 13) and to promote the education of consumers (#9-12), food service personnel (#14), school children (#15), and health professionals and their patients (#16). A final objective (#17) calls for a national system to monitor these and other indicators of nutritional status in the population.

Evaluation of Progress

The mid-course progress toward achievement of the objectives was examined in 1985.⁸ Of the 226 health objectives, 13% already had been accomplished by 1985

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**Department of Home Economics and Nutrition, New York University, 239 Greene Street, Room 537 East New York, NY 10003

and another 35% appeared likely to be achieved by 1990. For 26%, data were insufficient to permit evaluation and the remaining 26% seemed unlikely to be achieved by 1990.

Although inadequacies in formulation and measurement make evaluation of the nutrition objectives especially difficult, their progress appears to lag behind the health objectives as a whole. None of them had been achieved by 1985 but at least four, and possibly five, (#8, 9, 11, 17 and perhaps #5) seem likely to be attained if current trends continued. Six, however, appear unlikely to be accomplished at the current rate of progress (#2-4, 12, 15, 16) and another six (#1, 6, 7, 10, 13, 14) cannot be evaluated due to lack of data.

On the positive side, this summary indicates that Americans are increasingly aware of the importance of diet in reducing chronic disease risk factors (#9 and 11) and that the food industry is responsive to this trend (#12). Other gains have been noted in rates of breast-feeding (#8) and in development of a national nutrition monitoring system (#17).⁹

At the same time, significant problems are associated with both implementation and monitoring of the nutrition objectives. One overview of progress identifies unrealistically comprehensive expectations (e.g., #2, 12), inappropriate measurement data (#6) and lack of available baseline or national data as significant barriers to achievement and evaluation.¹⁰ Another notes the scientific and technical difficulties involved in designing appropriate nutritional goals, the paucity of data on the nutritional status of high-risk groups and the need for better methods to measure dietary changes and their effects on health.¹¹

Year 2000 Objectives

The final report on the 1990 objectives is expected in the early 1990s. By that time, development of new health objectives for the year 2000 will have been completed and plans for their implementation established. The planning process is coordinated by the PHS Office of Disease Prevention and Health Promotion in conjunction with the Institute of Medicine of the National Academy of Sciences. These agencies have encouraged participation from professional and voluntary organizations of health professionals, advocates and consumers through a series of regional hearings and meetings and through solicitation of written comments.

They have also established guidelines for drafting objectives; objectives are to be measurable, to be national in scope and to comprise concise statements of proposed achievement in six areas: health status, risk reduction, public awareness, professional education, services and monitoring.¹²

Nutrition continues to be included as a separate focus of this project and there is still ample opportunity for nutrition professionals to become involved. Draft objectives are scheduled for publication in the *Federal Register* in the summer of 1989, followed by a 90-day period for public comment. Publication is expected by the summer of 1990.¹²

Nutrition professionals should be involved at every stage of this process in order to make certain that the year 2000 objectives do not repeat the mistakes of the 1990 experience and that they reflect appropriate priorities and concerns.¹³

Summary

Development of nutrition objectives for the years 1990 and 2000 forms an important part of a national strategy to reduce preventable health risks. These initiatives present an opportunity for nutrition professionals to define priorities for nutrition in preventive health care and to establish the nation's nutrition policy agenda for the next decade.

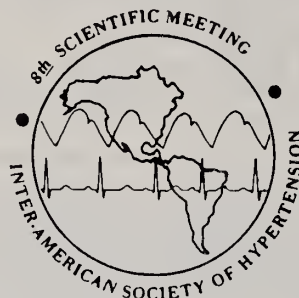
Note: Individuals and groups seeking information on how to participate should write to Coordinator, Year 2000 Objectives, Institute of Medicine, 2101 Constitution Avenue, NW, Washington, DC 20418.

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The work reported here was conducted while Dr. Nestle was Staff Director for Nutrition Policy, Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, DC.

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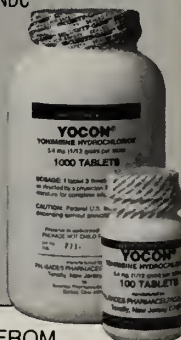
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Observaciones sobre el Comentario del Centro Cardiovascular de Puerto Rico y del Caribe

Aurelio Lladó*

Hemos leído con gran interés el "Comentario" sobre las realidades del Centro Cardiovascular de Puerto Rico y del Caribe publicado en las páginas 466 y 467 de la edición de diciembre de 1988 del Boletín de la Asociación Médica de Puerto Rico.

Nos agrada el que el Dr. Enrique Vázquez Quintana exprese su sentir sobre este asunto. Sin ánimo de evaluar todas las aseveraciones en el escrito, creemos que es importante aclarar algunos conceptos vertidos en el mismo que podrían crear opiniones equivocadas en el lector.

Participación de Cirujanos en la Confección de la Legislación

En el segundo párrafo del escrito se dice y citamos: "Es interesante notar que la legislación mediante la cual se creó el Centro Cardiovascular de Puerto Rico y del Caribe fue redactada por no cirujanos y sin la participación de cirujanos cardiovasculares y generales" (traducción nuestra). Nos extraña esta aseveración del autor, ya que es de conocimiento público que la propuesta inicial para el desarrollo de dicho Centro Cardiovascular fue elaborada por un comité compuesto por el Dr. Mario R. García Palmieri, Profesor Distinguido y Jefe de la Sección de Cardiología de Adultos de la Escuela de Medicina de la Universidad de Puerto Rico, el Dr. Arturo Medina Ruiz, Catedrático Asociado en Medicina y miembro del Laboratorio Cardiovascular No-Invasivo del Hospital Universitario, Dr. Angel F. Espinosa, Catedrático Asociado de Pediatría y Director de la Sección de Cardiología Pediátrica del Hospital Pediátrico Universitario, la Dra. Migdalia González, Catedrática Auxiliar de Medicina y Directora de la Unidad de Cuidado Intensivo Post Quirúrgico del Centro Médico de Puerto Rico, el Dr. Efraín Defendini, Catedrático de Cirugía de la Escuela de Medicina y Jefe de la Sección de Cirugía Cardiovascular de la Escuela de Medicina y del Hospital Universitario, el Dr. José Eugenio López, Catedrático de Medicina, la Dra. Nydia R.

De Jesús, entonces Catedrática de Anestesiología de la Escuela de Medicina y Directora del Centro Cardiovascular del Centro Médico de Puerto Rico y la Sra. Laura E. Torres, Directora Ejecutiva de la Administración de Servicios Médicos. La participación del Dr. Efraín Defendini ha sido altamente valiosa y decidida en el desarrollo del proyecto.

El Funcionamiento del Centro Cardiovascular

El autor del comentario expresa que la forma de funcionamiento del Centro Cardiovascular no está clara y que nadie conoce cómo funciona. El Centro está aún a 24 meses de comenzar a funcionar. Esta observación podría ser juiciosa, ya que el Centro Cardiovascular de Puerto Rico y del Caribe ha sido desarrollado como una nueva modalidad de prestación de servicios a los pacientes cardiovasculares de Puerto Rico y el cual se sale de las organizaciones gubernamentales previas existentes en el país. Este nuevo concepto está orientado a ofrecer el mejor servicio de excelencia con profesionales bien capacitados al costo menos oneroso posible tanto para los pacientes indigentes como los pacientes del sector privado de Puerto Rico. Hay varios aspectos del funcionamiento a dilucidarse antes de comenzar su operación. Confiamos en que con la cooperación de los interesados en que el Centro triunfe habrá una institución de excelencia que funcione bien.

Relación del Centro y la Facultad del Recinto de Ciencias Médicas

Por razones obvias la legislación no podía entrar en los detalles finales de la relación a existir entre la facultad de la Escuela de Medicina de la Universidad de Puerto Rico y del Centro Cardiovascular. La intención de la Ley y de la Junta de Directores es que el Centro Cardiovascular sea un taller para enseñanza e investigación a ser utilizado por la Escuela de Medicina de la U.P.R. Las relaciones a establecerse entre la facultad de la Escuela de Medicina están siendo estudiadas hace varios meses por un comité de facultativos de la Escuela de Medicina nombrado por la Decana de la Escuela. Este comité tiene la tarea de definir las relaciones del Centro Cardiovas-

*Director Ejecutivo, Corporación del Centro Cardiovascular de Puerto Rico y del Caribe.

cular y la Escuela. Se ha reunido en cuatro ocasiones desde septiembre de 1988 y participan el propio doctor Vázquez Quintana como Jefe de Cirugía y los Jefes de Medicina, Pediatría, Anestesiología; los Jefes de Cirugía Cardiovascular de Adultos, Cirugía Cardiovascular de Niños, Cardiología Pediátrica y la Sección de Anestesiología Cardiovascular y los Jefes de los Laboratorios Invasivo y No-Invasivo y un representante de Cardiología de Adultos. Todos son miembros a jornada completa de la facultad de la Escuela de Medicina de la U.P.R. El doctor Vázquez Quintana conoce de este hecho, pero no lo menciona en su escrito a pesar de que él como Jefe del Departamento de Cirugía de la Escuela de Medicina ha asistido a las cuatro reuniones celebradas para atender este asunto tan importante. Obviamente se espera que el resultado de las deliberaciones de este comité sea un factor importante en la clarificación y elaboración de las relaciones de la facultad entre la U.P.R. y el Centro Cardiovascular. Este Comité rendirá un informe a la Decana de Medicina y ésta al Rector del Recinto de Ciencias Médicas quien a su vez someterá una propuesta a la Junta de Directores de la Corporación del Centro Cardiovascular.

La Junta de Directores del Centro Cardiovascular de Puerto Rico y del Caribe

Entendemos que pueden haber diversas opiniones en relación a la composición de la Junta de Directores del Centro Cardiovascular. La composición de una Junta de Directores puede variar de acuerdo a la filosofía de los redactores de la pieza legislativa, sin embargo, lo importante de la Junta de Directores en la Ley que crea el Centro Cardiovascular es que las funciones están bien claramente especificadas requiriendo tareas definidas a cumplirse en armonía con las recomendaciones del "Joint Commission on Accreditation of Hospitals".

El doctor Vázquez Quintana cuestiona además la presencia del Secretario de Salud en la Junta de Directores. Reconocemos su derecho a así hacerlo, pero estamos conscientes que, por mandato constitucional, el Secretario de Salud tiene la responsabilidad en Puerto Rico de todo lo relacionado a la salud de sus ciudadanos. Un Secretario responsable y bien informado, que conoce la operación de día a día del Centro Cardiovascular, puede llevar un mensaje más claro a las dependencias gubernamentales concernidas para lograr una asignación real de fondos para los servicios cardiovasculares a ser rendidos a los pacientes indigentes que son responsabilidad del Estado. La presencia del Rector del Recinto de Ciencias Médicas en la Junta de Directores tiende a garantizar que se cumpla la intención de la Ley en el sentido de que el Centro sea taller de enseñanza y de investigación para el Recinto de Ciencias Médicas de la Universidad de Puerto Rico. La presencia del Director Ejecutivo de ASEM garantiza la participación de uno de los ejecutivos gubernamentales más envueltos en la prestación de servicios de salud y responsable de la operación del Centro Médico de Puerto Rico donde geográficamente está ubicado el Centro Cardiovascular.

Los otros dos miembros de la Junta lo constituyen dos personas nombradas por el Gobernador a recomenda-

ción del Honorable Secretario de Salud quienes representan a la Sociedad Puertorriqueña de Cardiología y a una Fundación de Cardiología, de fines no pecuniarios, debidamente inscrita en el Departamento de Estado del Estado Libre Asociado de Puerto Rico.

Ley de Personal del Centro y el Discrimen

El Centro Cardiovascular de Puerto Rico y del Caribe para poder funcionar como una institución de primer orden tiene que tener la agilidad de ajustarse a las realidades para reclutar personal bien entrenado y con altas motivaciones de servicio a los pacientes. El que tenga un sistema de personal autónomo se ampara en conceptos modernos de administración y en el deseo de ofrecerle a la ciudadanía el servicio que ésta se merece. No se pretende bajo ninguna circunstancia el discriminar en el servicio rendido por esta institución sino por el contrario se pretende ofrecer en Puerto Rico a todos los puertorriqueños, la misma calidad de servicios que solamente los pudientes buscan en el extranjero.

Las Consultas en el Exterior

Esta correcto el doctor Vázquez Quintana al mencionar que un grupo de médicos, administradores, arquitectos e ingenieros visitaron varios centros del exterior cuando se comenzó el diseño del Centro Cardiovascular. Entre los médicos visitantes estuvieron los Dres. José E. López, Pablo I. Altieri, Angel F. Espinosa, Enrique Márquez y Efraín Defendini. Los últimos dos son cirujanos cardiovasculares de gran prestigio en este país. Además de estudiar la planta física hubo diálogo sobre la organización profesional. Como es de conocimiento del doctor Vázquez Quintana, se han establecido consultas con diferentes centros fuera de Puerto Rico solicitando información sobre aspectos profesionales y entre los planes de trabajo bajo consideración se han incluido visitas a varios sitios a estos efectos.

El desarrollo del Centro Cardiovascular es complejo y no tenemos la menor duda que con el respaldo de la Junta de Directores, con la ayuda del pueblo de Puerto Rico, el endoso decidido de la Legislatura y nuestro Gobierno, la buena fe de los funcionarios y la facultad de la Escuela de Medicina y de las clases profesionales del país se logrará una institución que será motivo de orgullo para todos y donde se alivie el sufrimiento de los pacientes cardiovasculares de nuestro país. Me siento confiado en que las observaciones aquí vertidas puedan ayudar a que los lectores tengan una visión más clara sobre el Centro y evitar en alguna medida conclusiones erradas que podrían estar basadas en apreciaciones distantes a la realidad.

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ACTIVOS

Abreu Román, Antonio M. MD - Escuela de Medicina de la Universidad Central de Madrid, España, 1954. Medicina Interna. Ejerce en Manatí.

Acevedo Acosta, Gilbert MD - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, República Dominicana, 1984. Medicina General. Ejerce en Aguadilla.

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Morales Martínez, Alcira MD - Escuela de Medicina de la Universidad Central de Venezuela, 1969. Medicina de Familia. Ejerce en Carolina.

Ordoñez González, Luis R. MD - Escuela de Medicina de la Universidad de Zaragoza, España, 1959. Medicina Interna y Cardiología Clínica. Ejerce en Fajardo.

Ortega Ortiz, Orlando MD - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1983. Medicina General. Ejerce en Salinas.

Pérez Martínez, Floren MD - Escuela de Medicina de la Universidad Central del Caribe, Cayey, 1980. Obstetricia y Ginecología. Ejerce en Cayey.

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Robles Cardona, Nelson A. MD - Escuela de Medicina de la Universidad de Santiago de Compostela, España, 1978. Medicina Interna, Hematología, Oncología. Ejerce en Bayamón.

Rodríguez Flores, Regino MD - Escuela de Medicina de la Universidad de Santiago de Compostela, España, 1974. Otorrinolaringología. Ejerce en Santurce.

Rodríguez Hernández, Luis Edil MD - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1981. Medicina Interna. Ejerce en Ponce.

Rojas Díaz, Fernando MD - Escuela de Medicina de la Universidad de Puerto Rico, 1978. Ortopedia. Ejerce en Río Piedras.

Rosa Sierra, José A. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1985. Patología. Ejerce en Ponce.

Rosario León, Guillermo Rafael MD - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1979. Nefrología y Medicina Interna. Ejerce en Guayama.

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Sibilia Sánchez, Galeno MD - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, 1976. Medicina General. Ejerce en Guaynabo.

Torres Cabret, Carlos MD - Escuela de Medicina de la Universidad de Sevilla, España, 1974. Medicina General. Ejerce en Santurce.

Vargas Bernal, Manuel I. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1979. Obstetricia y Ginecología. Ejerce en San Sebastián.

Yulián Valentín, Antonio MD - Escuela de Medicina de la Universidad de Puerto Rico, 1974. Urología. Ejerce en Cayey.

INTERNOS - RESIDENTES

Alcaraz Micheli, Luis G. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1987. Oftalmología.

Báez Torres, Lynette M. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1986.

Berrocal Fernández, María MD - Escuela de Medicina de la Universidad de Illinois, 1986. Oftalmología.

Chardón Feliciano, Domingo MD - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, República Dominicana, 1985. Medicina Interna.

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Henn Arvelo, Carmen MD - Escuela de Medicina de la Universidad de Puerto Rico, 1984. Oftalmología.

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REINGRESOS

Casanova Delgado, Miguel A. MD - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, República Dominicana, 1971. Pediatría.

Lowry, Philip C. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1971. Cirugía. Ejerce en Isla Verde.

Rivera Colón, Angel L. MD - Escuela de Medicina de la Universidad de Puerto Rico, 1968. Nefrología. Ejerce en Bayamón.

Rivera Vázquez, Radamés MD - Escuela de Medicina de la Universidad de Salamanca, España, 1960. Siquiatría. Ejerce en San Juan.

Rodríguez Noble, Juanita MD - Escuela de Medicina Pedro Hernández Ureña, República Dominicana, 1977. Pediatría. Ejerce en Bayamón.

Román Selva, José F. MD - Escuela de Medicina de la Universidad de Montpellier, Francia, 1957. Cirugía. Ejerce en Bayamón.

Torres Feliciano, José A. MD - Escuela de Medicina de la Universidad de Salamanca, España, 1967. Medicina de Familia. Ejerce en Isabela.



AMERICAN ACADEMY OF PEDIATRICS

ACP RECOMMENDS ULTRASOUND FOR GALLBLADDER EVALUATION

Ultrasound is the preferred initial test to detect gallbladder disease, according to "How to Study the Gallbladder," an American College of Physicians (ACP) recommendation published Nov. 1 in *Annals of Internal Medicine*.

Developed by ACP's Clinical Efficacy Assessment Project (CEAP), the recommendation states that in most cases physicians should first use ultrasound—sound waves that form two-dimensional images of internal body organs—to test for both acute and chronic gallbladder inflammation.

Gallbladder disease is a significant national health problem; more than 500,000 patients have gallbladders surgically removed each year in the United States, according to the paper.

ACP recommends ultrasound because the diagnostic technique is highly accurate in detecting gallbladder disease. Ultrasound can be performed more rapidly and at lower cost to the patient than other imaging tests, and is safer since it does not expose the patient to radiation, according to ACP.

CEAP evaluates nonsurgical medical tests, procedures and therapies, and makes recommendations based on safety, efficacy and cost. Since 1976, CEAP has provided physicians with more than 150 recommendations.

ACP MAKES RECOMMENDATIONS ON CARDIAC REHABILITATION

The American College of Physicians (ACP) recently recommended medically supervised physical exercise for certain patients recovering from heart attacks or heart surgery.

The recommendation, developed by ACP's Clinical Efficacy Assessment Project (CEAP), identifies patients at low, intermediate and high risk for future cardiac problems, and suggests appropriate levels of rehabilitation for each category. Electrocardiographic (ECG) monitoring and intensive supervision during exercise are recommended for high-risk patients. However, formal rehabilitation programs were found to be unnecessary for most patients who suffered uncomplicated heart attacks, according to ACP.

Cardiac rehabilitation should be tailored to each patient's needs, with the use of teaching, counseling and exercise programs determined on an individual basis by physicians, ACP stated. The recommendation was published Oct. 15, 1988 in *Annals of Internal Medicine*.

SPOILED CHILD SYNDROME INS'T PROPERLY UNDERSTOOD

People often speak of children being "spoiled" and parents worry that certain approaches to managing children may result in spoiling them. But a physician suggests that parents may worry excessively, and that behaviors viewed as "spoiled" may be normal or even stress-related actions.

"The common misconception is that children are spoiled by overindulgence, by being given too much—too much time, too much attention, too many things," says Bruce J. McIntosh, M.D., a physician at St. Vincent's Medical Center, Jacksonville, Florida.

But in fact, he says this is incorrect. "Indulging children is one of the joys of being a parent," he writes, in a special article in the January issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP). "When combined with a positive parental presence in the form of clear expectations and limits, it (indulgence) does not produce unpleasant, demanding children."

Indulgence can, however, result in spoiling when the parent attempts to meet the child's needs with material gifts and uncritical acceptance while failing to provide guidelines for acceptable behavior, Dr. McIntosh says.

The true "spoiled child syndrome" is characterized by excessive self-centered and immature behavior. These children show a lack of consideration for others, demand to have their own way, have difficulty delaying gratification and are prone to temper tantrums. Their behavior is manipulative and they are unpleasant to be around, even for those who love them.

Parents may be concerned that "certain behaviors are indications that a child is becoming spoiled when these behaviors are really unrelated to spoiling as properly understood," Dr. McIntosh writes. Age-related normal behavior patterns can take many forms:

- Young, healthy infants spend an average of 2 1/4 hours per day crying in the first seven weeks of life, and some infants cry much more, says Dr. McIntosh. "Parents may be reassured that they need not hesitate to comfort a crying baby because of fears of spoiling," he says.
- Toddlers have normal, natural curiosity, and many parents are unprepared for the intensity of this urge to investigate the environment. It isn't that the toddler is spoiled, but rather, wants to learn about the things around him. Dr. McIntosh suggests "child-proofing" the environment so parents can teach children the limits of what to touch and what not to touch.
- The so-called "terrible twos" can be a phase where the child is likely to exercise autonomy by resisting the efforts of others to guide and control his activities. Parents who are concerned their two-year old's behavior is a sign of spoiling can be helped to understand that it is an important, positive thing that the child has developed a "mind of his own."

"A variety of family problems are capable of producing behavioral difficulties in the child which might result in the perception that he or she is spoiled," Dr. McIntosh says. "These include marital discord, such as chronic verbal fighting or abuse, physical violence such as spouse or child abuse, and alcoholism or other substance abuse."

In a divorce situation, for example, Dr. McIntosh says that because of feelings of guilt, one or both parents may be reluctant to enforce the usual limits.

But many of these problem behaviors, and their misperception as signs of spoiling, can be corrected with appropriate anticipatory guidance.

More accurate examples of true spoiling are older infants who continue to demand 2 a.m. feedings, older infants who cry frequently in the middle of the night because they get rewarded with attention, and children who have frequent temper tantrums.

Dr. McIntosh says the first situation can be corrected by increasing the interval between daytime feedings, and not feeding infants every time they are held. In the second case, parents must stop responding to middle-of-the-night crying. "It is normal for infants to cry for 10 to 15 minutes as they settle down to sleep," Dr. McIntosh says. "Such crying will not hurt the baby." And temper tantrums, he says, should simply be ignored.

Finally, one general piece of advice recommended by Dr. McIntosh: "It is the consistency of the punishment, not its severity, that helps the child to learn the rules." An example is the use of "time-out." It can be successful because it is not severe and parents do not hesitate to invoke it consistently.

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Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquina a doble espacio; por un solo lado de cada página, en TRIPPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej. MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

Ilustraciones

Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

Resumen

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

- Para artículos de revistas: Apellido(s) e iniciales del nombre del autor(es), título del artículo, nombre de la revista, año, volumen, páginas. Por ejemplo:
Villavicencio R. Soplos inocentes en pediatría, *Bol Asoc Méd P Rico* 1981; 73: 479-87
Si hay más de 7 autores, incluir los primeros 3 y añadir et al.
- Para citación de libros donde el autor(es) del capítulo citado es a su vez el (los) editor(es): Apellido(s) e iniciales del autor(es), título del libro, número de edición, ciudad, casa editora, año y página. Por ejemplo:
Keith JD, Rowe RD, Vlad P. Heart disease in infancy and childhood, 3d. Ed., New York, MacMillan, 1978: 789
- Para citación de libros donde el editor(es) no es el autor(es) del capítulo citado se añade el autor(es) del capítulo y el título del mismo. Por ejemplo:
Olley PM. Cardiac arrhythmias. In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 275-301

Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquina a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

*Estas "Instrucciones para los Autores" son de acuerdo a las normas establecidas por el Comité Internacional de Editores de Revistas Médicas en sus "Requisitos Uniformes para Manuscritos Sometidos a Revistas Bio-Médicas".

INSTRUCTIONS TO AUTHORS*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

References

These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should be abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

- For periodicals: Surname and initials of author(s), title of article, name of journal, year, volume, pages. For example:
Villavicencio R. Soplos inocentes en pediatría. *Bol Asoc Méd P Rico* 1981; 73: 479-87
If there are more than 7 authors list only 3 and add et al.
- For books when the authors of the cited chapter is at the same time the editor: Surname and initials of author(s), title, edition, city, publishing house, year and page. For example:
Keith JD, Rowe RD, Vlad P. Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 789
- For chapter in book when the author of the chapter is not one of the editors:
Olley PM. Cardiac arrhythmias. In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed. New York, MacMillan, 1978, 275-301

Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

*The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".



STUDY SUGGESTS MULTIVITAMIN USE MAY PROTECT AGAINST FETAL DEFECTS

Women who use multivitamins around the time of conception may be reducing the risk of their fetuses developing neural tube defects (NTDs), such serious problems as spina bifida and anencephaly, a study in the *Journal of the American Medical Association* suggests.

However, both the report and an accompanying editorial urge caution in interpreting these provocative findings. Further research, they agree, is needed to clarify whether multivitamin use by pregnant women in fact offers a protective effect against development of these severe birth defects.

Spina bifida, incomplete closing of the bony casing around the spinal cord, and anencephaly, an absence of major parts of the brain, are the most common of the NTDs. There is some suggestion in the medical literature that women who have previously had fetuses affected by such problems, and thus are at increased risk of having another similarly affected pregnancy, can reduce that risk through periconceptional multivitamin use—that is, use in each of the three months before conception through the first three months of pregnancy.

The new report, by Joseph Mulinare, MD, and colleagues at the Centers for Disease Control (CDC), Atlanta, is the first large-scale, population-based study to evaluate this possible protective effect in women who may or may not have had a previous baby with a neural tube defect.

The study involved 347 babies with NTDs live- or stillborn from 1968 through 1980, and 2,829 control babies without birth defects. NTD babies were identified via the Atlanta Birth Defects Case-Control Study, which gathered information from parents of babies with serious malformations in the Atlanta area. Controls were randomly selected through birth certificates. Fourteen percent of mothers in the study reported periconceptional multivitamin use, 40 percent reported non-use.

The authors report an “overall apparent protective effect of periconceptional multivitamin use on the

occurrence of neural tube defects,” figuring that users had less than half the relative risk of non-users of having a baby with an NTD.

“If the protective effect of periconceptional multivitamin use suggested by our study is a true and direct effect, the finding would have significant public health and economic implications, since about 95 percent of (neural tube defects) in the United States occur in women who have not had a previously affected pregnancy,” the authors say. But “despite these demonstrations of an apparent protective effect of periconceptional multivitamin use,” they warn, “caution must be exercised in the interpretation of our results.”

Vitamins, they note, can also have an adverse effect on the fetus—vitamin A derivatives are known to cause birth defects, for example—so “prudence and counsel in considering the use of multivitamins is required.” In addition, they say, the data must be evaluated in light of potential methodological concerns and biases. Vitamin users differed from non-users in a number of “demographic, health-related and lifestyle characteristics,” they say.

“Nevertheless,” they conclude, “the results of this study clearly indicate differences in NTD risk between periconceptional vitamin users and non-users. At this time, it is not possible to say whether this difference is the direct result of multivitamin use or the result of other characteristics of women who use multivitamins. Further research is needed to clarify this important issue.”

In his editorial, Lewis B. Holmes, MD, of the Massachusetts General Hospital, Boston, calls the study’s finding an “exciting possibility” but echoes its caveats, saying that “such a simple solution is almost too good to be true.”

Holmes also takes note of the earlier published evidence—suggesting dietary factors are related to the occurrence of some NTDs, and the lack of definitive data. “Fortunately,” he adds, “a larger, randomized trial of the effectiveness of periconceptional vitamin supplements is under way in Great Britain. In the interim, this article... is the best evidence to date in the United States that periconceptional vitamin supplementation may help reduce the occurrence of anencephaly and spina bifida.”

JAMA December 2, 1988

LIFE-LONG HIGH CALCIUM INTAKE IMPORTANT FOR OSTEOPOROSIS PREVENTION

The amount of dietary calcium a woman has taken throughout her lifetime and her levels of endogenous female sex hormones appear to be two of the key factors predicting postmenopausal bone loss, says a study in the *Journal of the American Medical Association*.

A lifetime of adequate calcium intake coupled with

adequate levels of serum estrogens may maximize bone density after menopause, say the report's authors, Jane A. Cauley, DPH, of the University of Pittsburgh School of Medicine, and colleagues. The authors studied 174 postmenopausal women over a three-year period and looked for correlations between changes in bone density and dietary calcium intake, use of calcium supplements, and blood levels of estrone, the primary sex hormone in postmenopausal women.

The only protective effect found for calcium was in women reporting high 'lifetime' calcium intake. The relationship between life-long calcium intake and estrone levels was additive —women with both high estrone levels and high calcium intake had significantly greater bone density than women with less estrone and/or calcium intake, the authors report.

Osteoporosis, a condition marked by bone deterioration, frequently affects women after menopause when calcium is lost from bones more quickly than it is replaced. The resulting bone-weakening often leads to debilitating pain and fractures. Hormone replacement therapy with estrogen has been shown to help prevent the progression of osteoporosis. However, whether increased dietary calcium intake can prevent further bone deterioration remains unsettled, the authors say. "Calcium in the diet cannot substitute for estrogen in preventing bone loss, and its efficacy in preventing fractures is uncertain."

"These results confirm our previous pilot study of the positive relationship between estrone and bone and give further support to the view that serum estrogens play a role in the maintenance of bone integrity," the authors report.

Endogenous estrogens act directly on the body without being altered by the liver, as are orally administered estrogens. The authors say their findings help to establish the role of natural estrogens in preventing bone loss. They also believe their findings may also explain obesity's reported protective effects on bone loss. Fat cells are believed to be involved in estrone production, and the primary determinant of serum estrogen levels in the women studied was their degree of obesity, they report.

The authors found no significant relationship between the use of calcium supplements and bone density, and suggest the failure to find any positive relationship may be due to the fact that some calcium supplements often are not adequately absorbed.

"Our data suggest that high calcium intakes throughout life can preserve bone density," they say. But to have a beneficial effect, calcium intake must be in the "high range," which the authors define as slightly less than the current recommended daily allowance of 800 mg. It is still unclear, they say, whether high dietary calcium intake begun after menopause can prevent bone loss. The only group in which a protective effect of calcium was found was in women reporting high milk consumption both currently and during their periods of growth and development. "If anything, historical consumption may be more important than current consumption," the authors conclude.

"The greatest effect, however, was observed by combining both estrone concentrations with lifetime calcium intakes," they say. Either alone was not sufficient to

maximize bone density. If these findings are substantiated, they "would suggest that effective preventive approaches may be feasible both by increasing calcium intakes and by modifying factors that contribute to high estrogen levels especially in postmenopausal women," the researchers conclude.

JAMA December 2, 1988

SUNSCREENS MAY AFFECT VITAMIN D LEVELS IN ELDERLY

Elderly people who are long-term users of the sunscreen agent PABA (p-aminobenzoic acid) may be increasing their susceptibility to vitamin D depletion, a preliminary study in December's *Archives of Dermatology* suggests. The study by Lois Y. Matsuoka, MD, of the Jefferson Medical College, Philadelphia, and colleagues measured an index of vitamin D nutritional status, serum 25-hydroxyvitamin D, in 20 long-term PABA users (mean age 65) and 20 matched controls. The sunscreen group, who had used PABA for more than a year, had significantly lower serum vitamin D levels than the controls, although they were still mostly in the normal range. The authors say their results should not preclude use of sunscreens in skin cancer patients, but note their work "provides evidence for a hitherto unsuspected consequence of the overlap between the action spectrum of vitamin D formation and the absorption spectrum of PABA."

EFFECTS OF HYPERACTIVITY TREATMENTS ON GROWTH

Reports in December's *Archives of General Psychiatry* suggest treatment with the stimulant methylphenidate hydrochloride slows growth in hyperactive children while they take the drug, but not long-term. The two studies are by Rachel G. Klein, PhD, of the New York State Psychiatric Institute, New York City, and colleagues. One looked at the effects of withdrawing methylphenidate on 58 hyperactive children randomly assigned either to be taken off or to remain on the drug over two consecutive summers. No group height difference was found after one summer but, after two summers, those taken off the drug were significantly taller than the others. The second report studied 61 young adults treated with stimulants due to childhood hyperactivity, and found no height difference compared with 99 controls. The authors say a compensatory growth rebound seems to occur after stimulant therapy stops. "If medication is terminated in adolescence, the growth-limiting effect of methylphenidate, though real, is of greater physiological than clinical interest," they conclude.

DIARRHEAL DEATHS IN MANY AMERICAN CHILDREN CAN BE PREVENTED: STUDY

Diarrhea accounts for a small percentage of deaths among American infants and children each year, but many of these deaths probably could be prevented with targeted intervention efforts, a study in the *Journal of the American Medical Association* suggests.

Diarrheal deaths are most common among black infants in Southern states, reports the study by Mei-Shang Ho, MD, MPH, of the Centers for Disease Control (CDC), Atlanta, and colleagues. The South, therefore, "probably should be targeted for further studies and interventions," the report concludes.

Although diarrhea is a major cause of death in developing countries, such deaths in developed countries are believed to be relatively uncommon. To assess the importance of diarrheal diseases as a cause of preventable childhood death in the United States, the CDC researchers reviewed national mortality data for 1973 through 1983.

Diarrhea was reported as the cause of death for an average of 500 children aged one month to four years died each year, the study reports. These deaths were most common among children younger than one year of age, blacks, and those living in the South. Such deaths also were most common during the winter, probably due mostly to infection with rotavirus, and half the deaths occurred after a child had reached a medical facility.

Black infants studied were four times more likely to die of diarrhea than were white infants, "and this racial difference was observed consistently in every state and in all years studied," the authors report. What's more, they say, in some Southern states, "diarrheal mortality for black infants was 10 times that of whites." Interestingly, however, the greatest decline in diarrheal mortality between 1973 and 1983 also occurred in the South.

Looking in detail at fatal cases of infant diarrhea in Mississippi, the authors found such maternal factors as race, age, marital status, educational level and prenatal care were strongly associated with diarrheal death.

"Several results from this study suggest that many (diarrheal) deaths may be potentially avoidable," they conclude. "First, diarrhea seems to be the principle cause of death since the secondary diagnoses most commonly reported on the death certificates are recognized complications of diarrhea... rather than cancers or congenital defects, in which diarrhea may occur but be less of a contributor.

"Second, risk factors most significantly associated with diarrheal deaths are not neonatal conditions such as low birth weight or congenital anomalies but social factors, as suggested in this study, concerning race, maternal age, marital status, maternal education and prenatal care. While blacks are already known to have infant mortality twice that of whites, data from (this study) suggest that diarrhea mortality accentuates and magnifies this racial difference independent of birth weight," the report says.

The authors say multiple strategies will be needed to combat the diarrheal death problem. These deaths "deserve special attention" even though they are relatively few in number, because "in contrast to the situation for sudden infant death syndrome and congenital anomalies (the two leading causes of infant death), preventive measures for acute diarrheal deaths are well-known and readily available," the report concludes.

In an accompanying editorial, John Snyder, MD, of Children's Hospital, Boston, calls the CDC report "troubling," not only because of the wide availability of therapy for acute diarrhea but because of the greatly increased rate of diarrhea deaths among black children. "The most direct and immediate answer to this grave problem could be an effective program of education and use of (oral) glucose electrolyte solutions especially targeted at the high-risk infants and children identified by Ho et al," he writes. "As has been shown in other countries, this therapy can be highly successful even when administered by economically and educationally deprived populations. Such a program also might provide the stimulus for U.S. health care providers to adopt and practice a more uniform and thoughtful approach to the treatment of acute diarrhea.

JAMA December 9, 1988

ESTIMATING GESTATIONAL AGE

It's well-known that estimating gestational age by menstrual dating, that is, the mother's recollection of her last normal menstrual period, is fraught with error. But a report in the *Journal of the American Medical Association* looks at the potential extent of this error. Authors Michael S. Kramer, MD, of McGill University, Montreal, and colleagues, used early second trimester ultrasound measurements to test the validity of gestational age estimates based on menstrual dating in 11,045 women. For most deliveries that were at or near term, menstrual dating agreed with the ultrasound estimates within a week either way. But menstrual dating was way off in estimating pre- and postmaturity. "Nearly one-fourth of the infants who would be classified as premature based on (menstrual dating) are not in fact premature," the study says. "Far more striking is that only one-eighth of the infants classified as postterm based on (menstrual dating) are actually postterm." This has major implications for unnecessary induction of labor and cesarean sections, say the authors, who urge routine gestational dating with early ultrasound exams.

JAMA December 9, 1988

COLONY-STIMULATING FACTOR MAY SHARPLY LOWER CHOLESTEROL

Human granulocyte-macrophage colony-stimulating factor (GM-CSF) is a white blood cell growth factor that

is used in the treatment of bone marrow disorders. Now, a preliminary report in the *Journal of the American Medical Association* suggests it also might have profound cholesterol-lowering abilities. Authors Stephen D. Nimer, MD, and colleagues at the UCLA School of Medicine, Los Angeles, gave GM-CSF to eight patients with aplastic anemia in an effort to restore blood cell formation. They found that the patient's serum cholesterol levels decreased by an average of 37 percent during treatment, returning to baseline after therapy was ended. The authors can't explain the mechanism involved in this finding and say further studies of this effect are needed. But, they conclude, GM-CSF "may be potentially useful in the treatment of hypercholesterolemia and, possibly, in the prevention and treatment of atherosclerosis."

JAMA December 9, 1989

MRI OF THE HEAD AND NECK

Magnetic resonance imaging (MRI) has many useful applications in the head and neck region, but has its weaknesses as well, says a report by the AMA's Council on Scientific Affairs. The report, in the *Journal of the American Medical Association*, says MRI's major strengths include excellent soft-tissue contrast, multiplanar imaging ability, non-invasiveness and lack of ionizing radiation. MRI images likely will improve and its indications expand, says the report. But "the technology... remains relatively expensive," it adds, "and the additional information compared with that of other techniques might not always justify the difference in cost. Moreover, MRI's insensitivity to calcifications, lack of depiction of fine bone detail, and, in some areas, degradation caused by motion and other artifacts make computed tomography and other non-invasive studies more appropriate as a primary imaging tool in many circumstances."

JAMA December 9, 1989

REPORT SAYS REFUSAL TO PERFORM AUTOPSIES ON AIDS PATIENTS UNETHICAL

Pathologists are ethically obligated to perform clinically indicated autopsies on AIDS patients, says a report in the *Journal of the American Medical Association*.

Along with an increasing number of physicians who publicly refuse to care for patients infected with the AIDS virus, a number of pathologists are refusing to perform autopsies on AIDS patients "for reasons that prove illogical, prejudicial, or arbitrary," write authors Richard M. Ratzan, MD, and Henry Schneiderman, MD, of the University of Connecticut Health Center, Farmington.

"Physicians who arbitrarily pick and choose which risky patients they will serve violate the essence of a human service that includes the equitable acceptance of

reasonable risk," they write. "If adequate, established precautions can lower risk to a low, manageable level, as is true for AIDS, then refusals to care for such patients on the basis of risk become unnecessary and therefore unethical."

No one expects a physician to save a patient's life at the cost of his own, but it has long been recognized that caring for the sick can be a hazardous occupation, the authors say. "Although a doctor may not have an obligation to assume the personal risk of operating on an AIDS patient who wants a cosmetic rhinoplasty, the situation differs for a condition that is 'necessary,'" they write.

Autopsies are important for increasing medical knowledge, providing definitive diagnoses and information useful for relatives and those exposed to possibly contagious diseases, and for medical education, the authors say. Physicians voluntarily enter into the practice of medicine with clear knowledge of personal risk and, like firemen, are obliged to endure risks in the line of duty. "No free society forces a person to become a fireman or a physician; both professionals have knowingly made a risky choice," the authors say. "Taking care of any patient, alive or dead, in whom an obligation of care exists, and specifically including those with AIDS, comes down to a matter of common decency."

In a related commentary, Barbara Gerbert, PhD, and colleagues at the University of California, San Francisco, suggest reasons why fear of contracting AIDS persists in the medical workplace and how it can be best handled. "First, discussions about the extent of risk for HIV. Transmission should include a clear recognition that risk does exist and that concern is warranted," they recommend. "While the risks of contagion are low, they are still very real and infection control cannot be seen as negating the danger of HIV disease... Care must be taken not to present infection control as a panacea for health professionals' fear of AIDS."

As the facts about AIDS and HIV have changed, health care providers have lost confidence in the accuracy of the information they receive and in the motives of those conveying it, the authors say. Authorities should "clearly delineate what is known, what is unknown, and what is reasonable speculation," they say. "Health professionals' fear of getting AIDS persist as long as there is a risk that HIV can be transmitted in the workplace. The goal is not to eradicate that fear, but to prevent it from compromising the quality of patient care and from threatening the health professional's own well-being."

An accompanying report and editorial discuss the serious decline in autopsy rates and their growing importance as "postmortem audits." In the report, Hartmann H.R. Friederici, MD, of Northwestern University Medical School, Chicago, says "a veritable revolution in medicine" may be required to replace the current apathy toward the autopsy with the realization that the postmortem audit is an important index of medicine's efficacy in treating disease and of the quality of hospital care. "If medicine as a profession cannot resolve the matter of auditing deaths, outside agencies must be expected to force this issue," he warns.

"Quality assurance is now the thing that all health care institutions and all physicians are supposed to be doing," Says the editorial by *JAMA* editor George D. Lundberg, MD. "Product control with outcome indicators has been added to structure and process control as a measure of how well we physicians do our work. The routine autopsy is obviously a prime (indeed indispensable) method of assessing the outcome of clinical intervention."

JAMA December 16, 1988

PATIENTS RARELY ABUSE ANTI-ANXIETY BENZODIAZEPINE DRUGS. REVIEW INDICATES

Patients who are prescribed benzodiazepines for the relief of anxiety and insomnia rarely abuse these drugs, concludes a report in the *Journal of the American Medical Association*.

Some health professionals believe drug abuse and dependency may account for a substantial proportion of benzodiazepine use. But the study's authors, James H. Woods, PhD, of the University of Michigan Medical School, Ann Arbor, and colleagues, found no evidence to support this view in a review of the extensive medical literature on benzodiazepines.

Benzodiazepines, which include the widely used drug diazepam (Valium), are the most commonly prescribed drugs for treating anxiety and anxiety-related insomnia. "The vast majority of people actually taking these drugs do manifest the conditions for which benzodiazepine treatment is indicated and efficacious," the authors write. "There is virtually no recreational or other inappropriate use of benzodiazepines among patients for whom these drugs are prescribed."

"Surveys of patient populations have indicated that patients receiving prescriptions for one of the benzodiazepines or other minor tranquilizers or hypnotics tend to use less than prescribed and to reduce their use over time," they report. Patterns indicative of abuse, such as increasing dosage or increasing frequency of refills, are seen rarely, they say.

Reports of abuse, the report says, "probably reflect cases of individuals with histories of abuse of multiple drugs. These individuals represent a population distinct from the general population, including most patients who are candidates for benzodiazepine treatment. Most patients are not likely to develop 'psychological dependence' on these drugs and are not likely to acquire the inappropriate drug-taking behaviors associated with psychological dependence such as escalation of dose, obtaining prescriptions from multiple physicians, or taking the drug for reasons other than those for which it was prescribed," they conclude.

When benzodiazepines are abused, it is usually associated with a pattern of multiple-drug abuse, often involving alcohol and sometimes narcotics, say the authors; benzodiazepines are rarely the primary drug of abuse. "Patients who have histories of illicit drug use have the greatest likelihood of using benzodiazepines

inappropriately and, although they may have a justified need for these drugs, prescriptions for benzodiazepines for these patients should be accompanied by explicit warnings about their abuse potential, counseling about the effects of the drugs, and especially careful monitoring of the use of the drug."

While there is little risk of psychological addiction to benzodiazepines among non-drug abusers, some patients, who use the drugs for a long period of time, may develop mild physiological dependence, the authors report. For some patients, discontinuing the drugs after long-time use may lead to rebound anxiety and/or rebound insomnia. However, gradual reduction of dosage usually allows patients to discontinue the medication with minimum discomfort. There is no evidence that such physical dependence is accompanied by inappropriate drug-taking behavior, such as escalation of doses. "Most investigators agree that, when it is deemed appropriate to discontinue benzodiazepine treatment, patients can be tapered off gradually with few or no withdrawal symptoms," the authors conclude.

JAMA December 16, 1988

SPICY FOOD AND THE STOMACH

Eating spicy food might give some people heartburn, but it doesn't appear to cause visibly measurable damage to the stomach's mucosal lining in normal people, a study in the *Journal of the American Medical Association* says. They study, by David Y. Graham, MD, of the Veterans Administration Medical Center and the Baylor College of Medicine, Houston, and colleagues, used videoendoscopy to look at the stomach lining of 12 volunteers who ate four meals—one of bland food; another of bland food plus six aspirins; a spicy Mexican meal; and a pepperoni pizza. Except for single cases after the spicy meals, mucosal damage was seen only in those who ate the bland meal with aspirin. This, they say, "confirms earlier observations that administration of aspirin with food does not reduce the mucosal damage." Placing ground jalapeño peppers directly into the stomach also resulted in no mucosal damage after 24 hours.

JAMA December 16, 1988

NAIL PRODUCT CAUTION

A report in the *Journal of the American Medical Association* describes two cases of cyanide poisoning—one of them fatal—in children who accidentally ingested a solvent used to remove sculptured fingernails. Authors E. Martin Caravati, MD, of the University of Utah, Salt Lake City, and Toby L. Litovitz, MD, of the Georgetown University Hospital, Washington, DC, say this product contains the highly toxic solvent acetonitrile and can be confused with less toxic acetone-containing nail polish removers. This, in fact, occurred in one of the cases cited, that of a 16-month-old boy who died after

ingesting the nail-remover. The second cases involved a 2-year-old boy who survived with vigorous support care. Acetonitrile is metabolized by mammals into inorganic cyanide, the authors say. "Physicians and poison centers should be alerted to existence of this highly toxic product. We urge regulatory agencies to reconsider the wisdom of marketing a cosmetic that poses such an extreme health hazard," they write.

JAMA December 16, 1988

DIABETES' IMPACT ON HEART ATTACK SURVIVAL

Women have a much lower risk of fatal heart disease than men, but the odds shift sharply when diabetes is involved, a study in the *Journal of the American Medical Association* reports. The authors, Robert D. Abbott, PhD, of the National Heart, Lung, and Blood Institute, Bethesda, Md., and colleagues, used data from the long-term Framingham Study to analyze the impact of diabetes on recurrent heart attack fatal coronary heart disease in survivors of an initial heart attack. Among non-diabetics, the risk of fatal coronary heart disease was significantly lower in women than in men. But among diabetics, the risk of recurrent heart attack in women was twice that of men, the authors say. The effect of diabetes also doubled the risk of recurrent heart attack in women but had little effect in men. Female diabetics developed heart failure four times more often than women without diabetes. What's more, when heart failure developed, 25 percent of diabetic women suffered a recurrent heart attack or fatal coronary event, more than double the rate of non-diabetic women.

JAMA December 16, 1988

CYTOMEGALOVIRUS VACCINE FOR KIDNEY TRANSPLANT PATIENTS

A study in December's *Archives of Surgery* says transplant recipients at high risk of cytomegalovirus (CMV) disease can benefit from pre-transplant vaccination against CMV, the major viral disease-causing infection in renal transplantation. The authors, Kenneth L. Brayman, MD, of the Hospital of the University of Pennsylvania, Philadelphia, and colleagues, describe interim results of a double-blind, placebo-controlled trial of live, attenuated CMV vaccine in 172 transplant candidates followed for up to five years post-transplant. Eighty-eight patients received vaccine and 84 received placebo. Patients with the highest overall incidence of CMV disease were those who were CMV-seronegative before transplant but received a cadaver kidney that was CMV antibody-positive. The authors found no difference in the incidence of CMV infection or disease between the vaccine and placebo groups, but say the severity of CMV disease was significantly decreased in the vaccinated

high-risk patients versus those who received placebo. Graft survival also was much better in the high-risk vaccine group.

DIETARY FACTORS IN PARKINSON'S DISEASE

A study in December's *Archives of Neurology* suggests vitamin E might exert a protective effect against the development of Parkinson's disease. The study, by Lawrence I. Golbe, MD, of the University of Medicine and Dentistry of New Jersey, New Brunswick, and colleagues, involved a survey of 81 Parkinson's patients and same-sex married siblings without the disease. They were asked about the likelihood of their having eaten any of 17 food items between the time they married and age 40. While no item was associated with the presence of Parkinson's, the absence of the disease was associated with a preference for three items (nuts, salad oil or dressing pressed from seeds, and plums) that have higher vitamin E content than the other foods. Vitamin E, or alpha-tocopherol, is an antioxidant, and oxidative mechanisms are suspected of playing a key role in the development of Parkinson's disease, the authors say. But they agree that these conclusions are "provocative clues" and call for more detailed studies.

SEAT BELT LAWS REDUCE MORTALITY AND HEALTH CARE COSTS: STUDIES

The mandatory use of safety belts can significantly reduce motor vehicle accident injuries and deaths, as well as health care costs, conclude two studies in the *Journal of the American Medical Association*.

A study of motor vehicle accident injuries in North Carolina before and after the state's mandatory seat-belt law was implemented provides strong evidence that the law has achieved its purpose in reducing injuries, saving lives and cutting health care costs, say the authors, Terence L. Chorba, MD, MPH, of the Centers for Disease Control, Atlanta, and colleagues. They estimate that the North Carolina law may result in 1,100 fewer severe and fatal highway injuries per year.

The study examined crash data and injuries before the law went into effect, during a warning period, and after implementation of a fine for violators. It finds that a significant reduction in severe and fatal crash injuries among front-seat car occupants has occurred, especially since the fine went into effect. North Carolina's law became effective Oct. 1, 1985, although until Jan. 1, 1987, violators received only warnings. After that, front-seat occupants not wearing safety belts could be fined \$25.

Studies such as this can help legislators and voters "determine whether mandating buckling up is worth the inconvenience and sacrifice of personal freedom," the authors say. "This study indicates that the North Carolina law has reasonably achieved its legislative intent," the authors conclude.

The accompanying study, by Elizabeth Mueller Orsay, MD, of the University of Illinois, Chicago, and colleagues, indicates safety belt use can significantly reduce injuries and health care costs. The report is the first to use medical records rather than injury reports from police officers, the authors say.

The researchers studied 1,364 patients who were evaluated at four Chicago-area hospitals for traffic accident-related injuries. Of these, 791 (58 percent) had worn safety belts and 573 (42 percent) had not. Of the most severely injured, 81.8 percent had not worn belts at the time of injury. All five fatalities involved persons who were not protected, the authors report.

Only 6.8 percent those who had worn belts required hospital admission vs 19.2 percent of those who had not used belts. The mean charges for patients who had not worn belts (\$1,583) were nearly three times greater than those (\$534) incurred by patients who had, they report. "Thus, safety belt wearers had a 60.1 percent reduction in severity of injury, a 64.6 percent decrease in hospital admissions, and a 66.3 decline in hospital charges," they conclude.

Auto accidents are the leading cause of death in Americans aged 5 to 34 and the seventh leading cause of death overall, Orsay and colleagues write. In 1982, an estimated 3.2 million people were injured in auto crashes, of whom approximately 1.4 million were treated in emergency departments and 35,000 required hospitalization. The overall economic loss to the United States attributable to these accidents in 1980 has been estimated at \$57.2 billion. The Department of Transportation estimates that universal use of safety belts would reduce fatalities by 50 percent and injuries by 65 percent, the authors say.

More than 30 countries throughout the world have passed mandatory-use laws, the authors report. The United States is virtually the only developed nation that has not passed national safety belt legislation. To date, only 31 states and the District of Columbia have laws requiring safety belt use.

In an accompanying editorial, Diane Steed of the National Highway Traffic Safety Administration, Washington, D.C., says much more needs to be done to increase safety belt use in the United States, since more than half of America's motorists still drive unprotected. "I urge physicians and major health care providers, as part of their daily routine, to advise patients about the importance of safety belts and the use of child safety seats to prevent injuries from motor vehicle crashes," she writes.

JAMA December 23, 1988

HIGHER DRINKING AGE REDUCES DRUNK-DRIVING ACCIDENTS

Raising the legal drinking age to 21 can help reduce alcohol-related auto accidents among 19 and 20-year-old drivers, who appear resistant to the effects of stiffer drunk-driving penalties and anti-drunk-driving publicity,

a report in the *Journal of the American Medical Association* indicates.

Motor vehicle injuries cause nearly 40 percent of deaths among 15-to-24-year-olds; about half these deaths involve drunk drivers, says the study by Michael D. Decker, MD, MPH, of the Vanderbilt University School of Medicine, Nashville, and colleagues. Some states have responded to the drunk-driving problem by raising the minimum drinking age, boosting drunk-driving penalties, or both.

The *JAMA* study analyzed efforts to fight drunk driving in Tennessee, which boosted drunk-driving penalties in 1982 and raised its drinking age to 21 in 1984. Implementing tougher drunk-driving penalties was associated with a sharp drop in drunk driving among two of the three age groups the authors studied—15-to-18-year-olds and 21-to-24-year-olds. This effect persisted for nearly four years among the younger drivers, whose alcohol-related motor vehicle deaths fell 33 percent, but only lasted about a year among the older drivers, the authors say.

Interestingly, the threat of increased penalties for drunk driving had no influence on drivers aged 19 and 20. But raising the drinking age did, causing another "sudden and dramatic decline" in drunk driving in that age group—"an effect still present at the end of the study period," the authors say. Alcohol-related motor vehicle deaths fell 38 percent among the 19- and 20-year-olds.

"Special efforts to maintain awareness among high school students of the risks of (drunk driving), and its social unacceptability, would appear to have the potential for generating large benefits at a fraction of the effort and expense required to maintain such programs within society at large. Such programs should be supported and strengthened," the authors say.

JAMA December 23, 1988

DRUG CONTROVERSIES TOP YEAR IN MEDICINE 1988

Controversies over drugs—the familiar, the exotic, the dangerous, and the much-needed—dominated the Year in Medicine in 1988.

Other top medical news this past year included some key policy and scientific developments in the ongoing AIDS battle, intensified interest in the scope of misconduct and fraud in science, and renewed debate over euthanasia sparked by an essay in the *Journal of the American Medical Association*.

The drug debates began with a *New England Journal of Medicine* study suggesting that taking an aspirin every other day can greatly reduce the risk of heart attacks. But the study's caution that aspirin can have serious side effects in certain patients, and word of a related British study that did not offer such positive results, seemed to get lost among the news media and commercial hype sparked by the report. The Food and Drug Administration later issued strong cautions to aspirin makers and physicians not to over-sell aspirin's benefits.

A similar controversy followed when *JAMA* published a report suggesting that topical tretinoin (Retin-A), a long-used acne drug, could eliminate some of the wrinkles and other symptoms of sun-aged skin. This seemingly too-good-to-be-true report also caused a surge of media attention and demand for Retin-A. FDA Commissioner Frank Young, MD, eventually issued a strong statement reminding physicians and patients that the drug's anti-aging effects needed more study.

A related acne drug, oral isotretinoin (Accutane), also was the subject of debate following reports linking its use by pregnant women to a number of cases of birth defects even though the drug is not supposed to be used during pregnancy. Accutane, like Retin-A, is a derivative of vitamin A, which has long been known to have birth defect-causing potential in certain forms.

Controversy over the use of drugs —particularly steroids— in sports peaked when Canadian sprinter Ben Johnson was stripped of his Olympic gold medal after testing positive for one of these muscle-building substances. The furor focused new attention not only on the widespread use of these potentially dangerous drugs by professional athletes, who see them as a quick source of muscle bulk and strength, but also their apparent widespread availability to amateur athletes and others.

The FDA responded to demands that it streamline its process of making experimental drugs available to desperately ill patients for whom no other treatment exists. The FDA first announced that such patients would be able to import drugs not yet government-approved, and later announced plans to shorten the existing three-step drug testing process for agents showing promise against serious disease.

"This concept takes into account the need to weight the benefits of a new drug against the severity of the disease to be treated and the availability or absence of alternative therapies," AMA Executive Vice President James H. Sammons, MD, said of the FDA proposal to make the three-phase approval process more efficient. "We believe the proposed change affirms free and informed decision-making by patient and physician in cases where a drug with some risks may be preferable to the certain outcome of a disease."

Another drug debate seen in 1988 concerned the cost-effectiveness of a new blood clot-dissolving drug, tissue plasminogen activator, or TPA. At issue was whether TPA, which is much more expensive than another, older clot-buster, streptokinase, is worth the extra cost in treating heart attack patients.

The subject of fraud and misconduct in scientific research was examined in numerous reports in the scientific press and lay media this past year. Some within the scientific community cautioned that the debate not only was overblown but blurred the line between error, which is inherent in the scientific process, and deliberate misconduct. Others argued that the fraud cases underscore the problem of an increasingly competitive system of research funding and advancement that encourages cheating and sloppiness and resists self-correction. The debate was fueled by Congressional hearings and the first-ever indictment of a scientist accused of fraudulently obtaining federal research funding.

Euthanasia, a topic long-discussed in medical and lay circles, received renewed attention with *JAMA*'s publication of the essay, "It's Over, Debbie," in which an unidentified physician appeared to admit to the deliberate morphine-induced death of a young woman dying of cancer. The essay indicated that the physician met the patient for the first time shortly before giving her the injection.

The essay generated a legal debate that nearly dwarfed the discussion that *JAMA*'s editor sought to highlight by publishing it. State prosecutors sought to force the *Journal*, which agreed to publish the essay on the condition that its author not be named, to reveal the physician's identity, contending that a crime appeared to have been committed. Those efforts were rebuffed in court.

Letters to *JAMA* and other published reports overwhelmingly condemned the essayist's self-described actions and largely criticized the *Journal*'s publishing decision. The essay itself was attacked as ambiguous and undocumented; questions were raised about whether the author's actions, as described, were sufficient to cause death. There even were suggestions that the essay was fictional.

The AIDS toll continued to mount in 1988, with the Centers for Disease Control's cumulative case total topping 80,000 by year's end. Two major AIDS reports were released in 1988, including that of the Presidential Commission on the HIV (human immunodeficiency virus) Epidemic. Among the panel's more than 700 proposals was a call for strong anti-discrimination safeguards for those infected with HIV, as well as a recommendation for more funding for research, treatment and education. A related report by the National Academy of Sciences' Institute of Medicine also called for additional funding and for AIDS education efforts to become a priority nationwide, not just in "high-risk" areas. The year also saw increased concern about HIV transmission through intravenous drug use and the problems of HIV-infected babies, many of whom spend most of their short lives in hospitals.

On the research side, there was word that HIV can "vanish" following infection and remain undetectable for years, underscoring the need for more sensitive detection methods. There also were reports confirming the ability of zidovudine, (formerly AZT), to greatly improve AIDS patient survival, and studies describing an exciting new animal model for research on AIDS and other immune system abnormalities —mice into which a human immune system can be implanted.

Other major medical stories in 1988:

- Release of a Harvard study, the Resource-Based Relative Value Scale, proposed as a possible system for reforming Medicare reimbursement to physicians.
- An explosion in consumer demand for oat bran following studies suggesting such soluble fiber could be an inexpensive means of lowering serum cholesterol.
- New emphasis on the shortage of nurses in the nation's hospitals following an AMA proposal to create a new category of health care worker, the Registered Care

Technologist, and a federal commission's report on the shortage.

- Concern over the accuracy of Pap smears and other clinical laboratory tests following a Pulitzer Prize-winning series of *Wall Street Journal* articles.

- Debate over the use of fetal tissue and organs from anencephalic newborns in research and therapy.

- Efforts to limit medical resident's on-duty hours and improve attending physician oversight of physicians-in-training.

- Reevaluation of the efficacy of brain implants for the treatment of neurological disorders, particularly Parkinson's disease.

- Final FDA approval, after years of study and experimental use, of topical application of the antihypertension drug minoxidil to treat baldness.

- Appointment of Nobel laureate James Watson to head the massive, federally funded project to map and sequence the human genome.

SEXUAL BEHAVIOR OF ADOLESCENTS AND AIDS RISK

General AIDS education efforts may not necessarily translate into less risky sexual behavior among adolescents, says a letter in the *Journal of the American Medical Association*. In the letter, Steven E. Keller, MD, of the New Jersey Medical School, Newark, and colleagues say they interviewed 73 inner-city adolescents and young adults about their knowledge and attitudes about AIDS; their sexual history and current sexual behavior were also assessed. The youths' level of knowledge about AIDS was high, the authors say, but those who were sexually active also scored high on a scale of sex risk behaviors, suggesting that further "passive programs" focused on increasing AIDS awareness "are unlikely to substantially reduce sex risk behaviors in sexually active adolescents." The authors are testing an alternative, individualized educational program, designed around a subject's specific risk behaviors, and say preliminary evidence suggests this works much better.

JAMA December 23, 1988

PREVALENCE OF OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) appears to be far more common in the United States than previously believed, with prevalence rates up to 60 times higher than indicated in earlier studies, says a report in December's *Archives of General Psychiatry*. The authors, Marvin Karno, of University of California, Los Angeles, and colleagues, measured the prevalence of the disorder in more than 18,500 people in five communities as part of a National Institute of Mental Health program. The authors say 468 people qualified for an obsessive-

compulsive diagnosis at some point in their lives, for an average prevalence of 2.5 percent. Rates ranged from 1.9 percent to 3.3 percent over the five sites—40 to 60 times the rates estimated from previous clinical studies, the authors say. "Although not conclusive, the evidence is strong that OCD is a common mental disorder that, like other stigmatized and hidden disorders in the past, may be ready for discovery and demands for treatment on a large scale," they conclude.

LEECHES CAN BOOST MICROCIRCULATORY BLOOD FLOW

There is renewed interest in the use of leeches in medicine, specifically, using these anticoagulant-producing animals to maintain blood flow to skin flaps utilized in plastic and reconstructive surgery. Until now, however, there apparently has been no objective measurement of the vascular benefits of using leeches to support a flap compromised by congested blood flow. But a report in December's *Archives of Otolaryngology-Head and Neck Surgery* documents this effect in an animal model. Authors Richard E. Hayden, MD, CM, FRCS, of the Washington University School of Medicine, St. Louis, and colleagues used a sophisticated technique called doppler laser perfusion monitoring (DLPM) to gauge blood flow changes in pig skin flaps compromised by venous congestion. Applying leeches to nine such flaps led to significant increases in blood flow, the authors say. "To our knowledge, this represents the first report of objective quantification of blood flow changes in venous congested tissue leached by (the medical leech)."

COLOR CONTACT LENS CAUTION

Colored soft contact lenses are becoming increasingly popular, but this new eyewear might affect peripheral vision in some patients, cautions a report in December's *Archives of Ophthalmology*. The authors, Michael S. Insler, MD, of the Louisiana State University Medical Center School of Medicine, New Orleans, and colleagues, performed visual field testing on 10 patients with normal vision wearing a recently introduced colored soft contact lens. All but one patient experienced visual field constriction, or decreased peripheral vision, ranging from 5 to 20 degrees, the authors say. Overall peripheral visual field loss ranged from 21 to 47 percent. The problem may be due to the opaque colored dots applied to the lens periphery to give it its blue, green or aqua color. The authors say their experience with soft colored contacts generally has been favorable, but note that the lenses must be fitted carefully and that "fitters and patients should be warned of the possible constriction in visual field."



VASOTEC

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSO) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx (likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION). Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause granulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause granulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General:* **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: *Patients on Diuretic Therapy:* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucoside, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSO) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of 14 C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostatic hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

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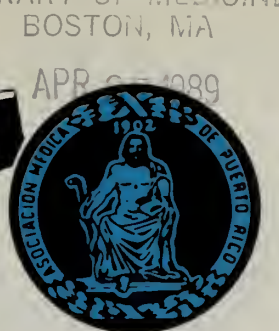
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Nuestra Portada

NUESTRA PORTADA

Nuestra Señora Madre de la Divina Providencia. Dibujo realizado por el artista A. Gantes teniendo por modelo la imagen original que fue traída a Puerto Rico en el año 1852 y que se encuentra en la Catedral de San Juan.

En el mes de la Semana Santa la Junta Editora quiso adornar la portada de nuestro Boletín con la imagen de la Virgen Patrona y Protectora nuestra a la que millones de puertorriqueños profesan devoción.

Con relación a esta devoción nos escribe la doctora Annette Pagán-Castro:

"La devoción a la Virgen de la Providencia se inicia en el año 1267 cuando San Felipe Benicio la invoca, ya que los frailes del Convento de Arezzo, Italia, estaban pasando hambre; era tiempo de guerra y gran escasez y milagrosamente aparecieron alimentos en la puerta del Convento.

El 19 de noviembre de 1493, hace 495 años, Cristóbal Colón divisó las montañas de nuestra Isla, este fue un suceso Providencial en nuestra historia. El 12 de octubre de 1851 el Obispo Don Gil Esteve, elige el título de María Madre de la Divina Providencia bajo cuyo patrocinio estará la Catedral y la Diócesis de Puerto Rico. En 1892 se declara la fiesta oficial de Puerto Rico y se elige como Patrona y Protectora de Puerto Rico.

Pequeños, entre los pueblos del mundo, somos como el niño que descansa apacible en la falda de su amorosa madre.

Hemos logrado llegar a ser lo que somos, por esta confianza que hemos tenido en Dios providente y en la Virgen María, a quien el mismo Dios ha confiado su único hijo.

¡De cuantas tragedias, guerras, huracanes y desastres nos hemos visto libres por la Providencia Divina!"

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico agradece la colaboración de la Dra. Pagán-Castro y de la Dra. Lillianne Ferrer quien consiguió el dibujo que reproducimos en la portada.



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There are no known contraindications to the use of sucralfate

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Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

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1 Eliakim R, Ophir M, Rachmilewitz D. *J Clin Gastroenterol* 1987;9(4):395-399

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“Joining the Army Reserve enabled me to take advantage of a number of conferences, including one at Walter Reed, where I worked with thoracic surgical colleagues, while conducting my own research project.”

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RESUMEN DE PONENCIAS (CALL FOR ABSTRACTS)

El Comité del Programa Científico invita a enviar resúmenes de ponencias de trabajos originales para considerarse para presentación durante la sesión científica que se efectuará los días 13, 14 y 15 de octubre de 1989.

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Fecha límite para entregar los trabajos: 31 de mayo de 1989

DERMATOLOGY DIAGNOSIS

Aida Lugo-Somolinos, MD
Jorge L. Sánchez, MD

This is the case of a 65-year-old female with history of diabetes and hypertension treated with chlorpropamide, chlorothiazide and prazosin hydrochloride, who three weeks prior to her visit to the University Hospital, developed fever, general malaise and swelling of the face accompanied by a skin eruption on the periorbital area, arms and neck. She was evaluated by a private physician who prescribed her some medications, but the patient continued deteriorating, and two weeks later developed progressive weakness of the shoulders and hip muscles.

On physical exam, the patient showed a temperature of 38.3°C and blood pressure 140/90. She was seen to have edema of the facial and periorbital regions and erythematous-violaceous patches with poikilodermatous changes on the face, V of chest, extensor areas of arms, dorsa of fingers and knees. There were telangiectases on the periungual areas.

Examination of the proximal muscles of the arms and legs showed moderate tenderness to palpation and decreased strength at the fair level.

Laboratories disclosed normal CBC, urinalysis and SMA-6. Abnormal findings included CPK 1,800u; LDH 340u; SGOT 89u; aldolase 10.3u, and a positive antinuclear antibodies test.



WHAT IS YOUR DIAGNOSIS?

- A) Hypothyroidism
- B) Systemic lupus erythematosus
- C) Dermatomyositis
- D) Trichinosis

DERMATOMYOSITIS

Dermatomyositis is a diffuse inflammatory and degenerative disease of striated muscle which causes symmetric weakness and atrophy of the proximal muscles in association with a variety of inflammatory cutaneous lesions. Polymyositis represents the same disease, except for the absence of skin lesions.

This group of diseases can be classified in five different types:¹

- Type I : typical polymyositis
- Type II : typical dermatomyositis with malignancy
- Type III : typical dermatomyositis with malignancy
- Type IV : childhood dermatomyositis
- Type V : Myositis associated with overlap syndromes

Dermatomyositis is most common in women, with a female to male ratio of 2:1, and may occur in childhood as well as in middle age.²

The cause of dermatomyositis is unknown, although it is usually associated to the connective tissue disorders with which it shares several features: rheumatic symptoms, cutaneous lesions, and serologic abnormalities. The onset can be related to some drug intake such as penicillamine and clofibrate.³ Cell mediated hypersensitivity appears to play a major role in the pathogenesis of dermatomyositis. Lymphocytes and lymphokine-mediated tissue injury could account for the pathologic features in adult dermatomyositis and polymyositis. Questions that need to be answered in regard to cell-mediated hypersensitivity in this disorder are 1) does muscle contain a specific autoantigen and 2) is there an immunogenic infectious agent or an antigen that cross-reacts with an infectious agent to which the patient is sensitized?²

Dermatomyositis can be associated to internal malignancy in up to 25% of the cases.⁴ Individuals with cancer and dermatomyositis are able to produce antibodies to their tumors, but there is no evidence that they are causally related to the myopathy.

The disease usually begins with erythema and swelling of the face and eyelids, the latter being first involved becoming swollen and pinkish-violet producing the so called heliotrope sign.⁵ The cutaneous lesions consist of erythematous-violaceous patches with slight edema which gradually extend to involve the upper chest, extensor surfaces of the extremities, particularly the knees, elbows, knuckles (Gottron's papules) and the distal portions of the fingers.⁶ Other features may include periungual telangiectasias; Raynaud's phenomenon (30%),⁵ calcinosis cutis (which is most common in childhood dermatomyositis), alopecia, photosensitivity and sclerodermatous changes.

The histopathology of the skin may vary depending on the type and stage of the lesions. It may show only non-specific inflammation, but frequently show histologic changes indistinguishable from cutaneous lupus erythematosus.⁵ These changes consist of flattening of the epidermis, hydropic degeneration of the basal cell layer, edema of upper dermis and a scattered inflammatory cell infiltrate. It can be differentiated from systemic lupus erythematosus (SLE) by direct immunofluorescence

studies which will show the presence of immunoglobulins at the dermoepidermal junction (lupus band test) in SLE, but not in dermatomyositis.⁶

Muscle involvement appears later, although it can be in the initial manifestation. The proximal muscles are involved in a symmetrical fashion causing muscular pain and weakness. The ocular muscles are rarely affected. Dysphagia can be present due to the involvement of upper esophageal muscles and cardiac involvement may occur in very severe cases. When there is no muscle involvement, the term amyopathic dermatomyositis has been used.

Childhood dermatomyositis differs from the adult one in that early muscle involvement, extensive and early calcinosis, and vasculitis are more prominent.⁵ There is usually a preceding respiratory illness² and absence of some features such as Raynaud's phenomenon and the sclerodermatous changes.

The association of adult onset dermatomyositis with internal malignancy has been reported frequently. Incidence varies from 15 to 50%² in some reports. It is most commonly associated to dermatomyositis than to polymyositis, and the skin and muscle manifestations can precede the carcinoma by several years. Adenocarcinomas of lung and breast have been the most frequent neoplasms associated to adult dermatomyositis.⁴

Laboratory findings are variable but they usually disclose abnormal levels of muscle enzymes such as serum aldolase, creatine phosphokinase, lactic dehydrogenase and serum glutamic oxaloacetic acid. Urinary excretion of creatine is increased and creatinine is decreased.⁵ Erythrocyte sedimentation rate may be elevated and the antinuclear factor is present in many patients.²

Electromyographic changes may include an unusual irritability on insertion of electrodes, presence of pseudomyotonic discharges, positive sharp waves and spontaneous fibrillation at rest. The electromyogram may be normal in 20-30% of cases.³

A muscle biopsy should be obtained from a muscle that is weak or tender, avoiding those used in the electromyogram. The characteristic microscopic features is a segmental necrosis within muscle fibers with loss of the cross-striations and a waxy or coagulative type of eosinophilic staining.³

To make a definite diagnosis of dermatomyositis, at least two of the three major laboratory criteria should be present in a patient with the typical skin lesions and proximal muscle weakness. These are elevated serum muscle enzyme levels, characteristic electromyographic changes or a diagnostic muscle biopsy.³

The differential diagnosis includes SLE, use of drugs such as penicillamine or clofibrate, hypothyroidism, muscular dystrophies, myasthenia gravis and active muscle infestations such as trichinosis.³

The treatment must include complete bed rest and the rapid administration of prednisone. The initial dose varies from 0.5 to 1.0mg/kg/day.³ As soon as the muscle enzymes approach normal, a tapering down of the prednisone should be started. Improvement of muscle strength begins 2-4 weeks later. The response is usually satisfactory in patients with no associated malignancy. If there is no improvement in 4-6 weeks, other options are

available such as methotrexate, cyclophosphamide or plasmapheresis.

The course and prognosis is usually favorable, especially on children. The most ominous sign is the presence of an associated malignancy, so all patients over 50 years-old who develop dermatomyositis should be investigated for this possibility.³

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Basal and Squamous Cell Carcinoma of Skin

Norma I. Cruz, MD, FACS

Skin cancers are the most common tumors in Puerto Rico and the United States. Here in the Island the incidence is .525 per 1000 population,¹ therefore being more frequent than breast or prostate carcinomas.

Of all cutaneous malignancies reported in 1981¹ for Puerto Rico, 78% were basal cell carcinomas, 20% were squamous cell carcinomas and the remaining 2% was made up of melanomas and other less common malignancies.

Basal and squamous cell carcinomas are most common on the head and neck, especially in fair-haired, fair-skinned, blue-eyed individuals. They are more prevalent in people who sunburn easily and who spend a lot of time outdoors, and are extremely uncommon in Blacks.

Squamous cell carcinoma (SQC) of the skin has a direct correlation with sun exposure, while fully one-third of basal cell cancers will arise in parts of the body that receive little or no sun exposure. Both kinds of lesion may develop in areas of scarring from burns, sinus tracts, vaccinations, etc.

The usual site of origin of a basal cell carcinoma (BCC) is the pluripotential epithelial cell present in surface epidermis or hair follicle. Squamous cell lesions arise from the malpighian or squamous cell layer of the epidermis.

As you will remember, normal skin (Fig. 1) is organized into 4 layers.

- (1) The basal cells form a single layer, are columnar in shape and have deeply basophilic cytoplasm. These are the pluripotential cells which can give origin to basal cell carcinomas.
- (2) The squamous cell layer is made up of polygonal cells which are arranged in a mosaic usually five to ten layers thick. They become flattened toward the surface, with their long axis arranged parallel to the skin surface.
- (3) The granular cell layer is made up of diamond-shaped or flattened cells that have a cytoplasm filled with keratohyaline granules that are deeply basophilic.
- (4) The horny layer results from the full keratinization of the cell which renders them anuclear. This layer stains eosinophilic.

After discussing the histology of normal skin the next step in understanding the physiopathology of skin malignancies is obtaining a working knowledge of the effects of solar or ultraviolet radiation on skin.

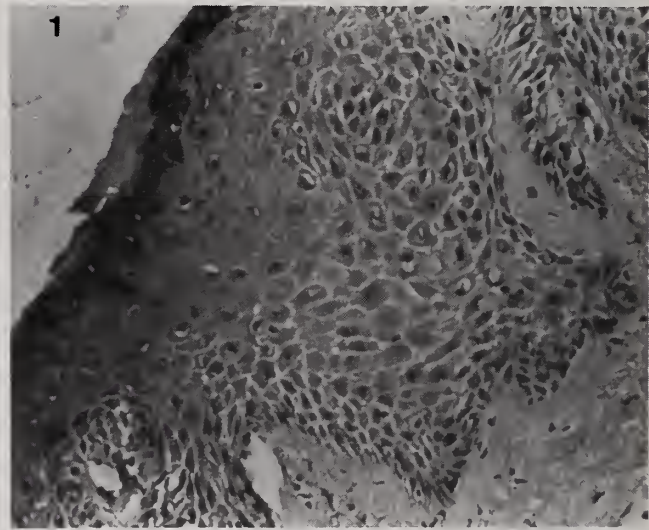


Figure 1. Normal epidermis in which the organization into layers can be identified: (1) basal layer, (2) squamous cell layer, (3) granular layer and (4) horny layer.

(Hematoxylin and eosin stain, original magnification x 400).

Ultraviolet Radiation

The electromagnetic spectrum may be divided into ultraviolet radiation, visible light, and infrared radiation. The ultraviolet band is further divided into UVC (1-290nm); UVB (290-315nm), and UVA (315-400 nm).² From 400 to 700 nanometers we have the bands of visible light, and above 700 nm, the infrared rays.

These wavelengths of nonionizing radiation can be produced by a variety of artificial radiant sources, but clinically we are most concerned with ultraviolet radiation generated by the sun and, in these hi-tech days, by sunlamps and tanning beds. The amount of radiation generated by fluorescent bulbs and other "cool" sources is of no clinical significance.³

The solar radiation that penetrates to the surface of the earth is almost devoid of UVC. The ozone-rich stratosphere effectively absorbs UV wavelengths below 290 nm, so that only UVB (280-315 nm) and UVA (315-400 nm)

reach the earth's crust. Over 95% of solar UV radiation is in the UVA waveband, while the small amount of UVB present is responsible for acute sunburns as well as much of the chronic sun damage and malignant degeneration occurring in human skin.

Epstein⁴ reviewed many of the factors involved in the production of skin cancer by ultraviolet light. Although UVB rays are the most carcinogenic, UVA rays are known to markedly accentuate the acute damage caused by UVB, enhancing its carcinogenic effect.⁵ More recently Strickland further showed that UVA rays, in and of themselves, are carcinogenic in mice, although far less than combined UVB/UVA radiation.

Infrared energy also seems to accelerate the carcinogenic process. Animals kept in a heated environment develop tumors more rapidly than those in temperature climates.⁶ Wind and high humidity increase the amount of UV damage and the rate of tumor formation. The condition known as erythema abigne, caused by chronic exposure to radiant heat, closely simulates chronic UV-radiation injury.

Fisher and Kripke⁷ have demonstrated that chronic subcarcinogenic UV radiation exposure increased the susceptibility of mice to transplantation with highly antigenic, UV-induced cancers. This finding suggests a systemic effect on suppressor T-cells for specific UV-induced tumor antigens. Based on animal studies, Kripke⁸ postulates that exposing skin to ultraviolet radiation has systemic immunologic consequences and that some of these immunologic effects are important in the pathogenesis of human skin cancers. The action spectrum for this effect falls primarily in the UVB range (between 275 and 350 nm).⁹

Sunscreens

The single most important and limiting factor in protecting our skins from ultraviolet radiation is the amount of melanin in the skin. Urbach¹⁰ studied the geographic distribution of skin cancer and concluded that a person's susceptibility to radiation-induced tumors is inversely proportional to the melanocyte content of his or her skin. Individuals of Celtic ancestry do not tan well, tend to sunburn with solar exposure, and are prone to develop skin cancer.

A number of topical agents have been promoted to combat the effects of UV radiation. They fall into two major classes, the physical reflectors and the chemical absorbers. The reflectors include compounds such as titanium dioxide and zinc oxide, which reflect all wavelengths of the UV spectrum. While effective, these are opaque creams, highly visible and cosmetically limiting. Among the chemical absorbers are preparations of para-aminobenzoic acid or its esters and the benzophenone group of drugs.

The various sunscreen products are rated by their sun-protective factor (SPF), i.e., the amount of UVB energy required to produce a minimal erythematous reaction through the product, measured as a factor of the same amount of energy for an equal reaction without sunscreen. The highest SPF needed under normal outdoor conditions is 15.

Basal Cell Carcinoma

Clinical Types

Nodular BCC begins as a flesh-colored nodule on the surface of the skin with small telangiectatic vessels coursing throughout (Fig. 2). On initial presentation it seems so innocuous that it may be easily mistaken for a dermal nevus or other benign skin tumor.



Figure 2. Nodular basal cell carcinoma over the medial canthal area of the patient.

The so-called rodent ulcer resembles nodular BCC except that it undergoes central ulceration. It tends to be more deeply seated, and characteristically presents as a slowly enlarging ulcer surrounded by a rolled pearly border. Superficial BCC is flush with the skin, erythematous, scaly, and on careful examination there may be a thread-like circumference. Some may have a shallow ulceration or crusting while others may show atrophic scarring. These lesions are frequently confused with eczema or fungal infection. (Figs. 3, 4).

Pigmented BCC differs from the nodular variety in its brown pigmentation. Sometimes the color is quite intense and deep, appearing on the surface as almost blue-black, and for this reason is often confused with a malignant melanoma. (Figs. 5, 6, & 7).

Morphea-like or sclerosing BCC presents as a firm, white or yellowish plaque with an illdefined border. Patients tend to describe it as an "enlarging scar" for which there is no antecedent history of trauma. This lesion is frequently misdiagnosed and should be watched for carefully. There is always induration but almost never ulceration, and the tumor may grow quite large without elevating more than one or two millimeters above the skin surface.

Histologic Types

The most common histologic presentation of basal cell carcinomas is that of tumor masses of various sizes and shapes embedded in the dermis, the peripheral cell layer of the masses shows a palisade arrangement, whereas the

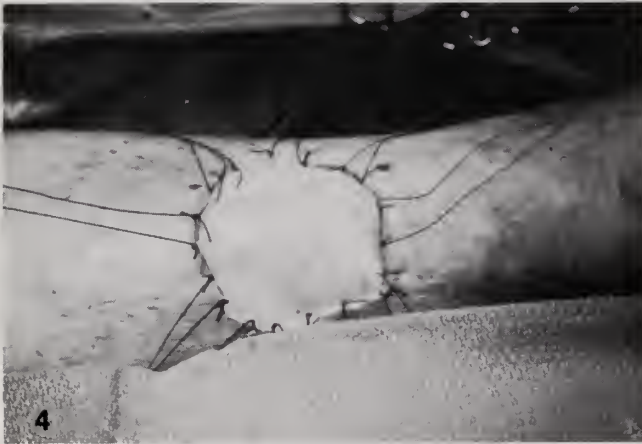


Figure 3 and 4. Superficial basal cell carcinoma over the middle third of the patient's leg and the resection followed by reconstruction using a split thickness skin graft.



Figures 5, 6 and 7. A patient with a pigmented basal cell carcinoma over the nasal tip. The lesion was surgically removed and the defect was reconstructed with a frontonasal flap.

nuclei of the cells inside lie in a haphazard fashion (Fig. 8).

Histologic types of basal cell carcinomas conform for the most part to the clinical types discussed above: superficial, nodular, nodular ulcerative, ulcerative, infiltrative and morphea-like.

There has been a great deal of debate in the literature over the aggressive nature of the various types, particularly the ulcerative and infiltrative. Jacobs, Rippey, and Altini¹¹ conclude that aggressive tumors are characteristically more ulcerative than infiltrative.

The differences between nodular, nodular ulcerative and ulcerative tumors are unclear; perhaps the classifications reflect variations in the host response rather than in the tumors themselves. There is no doubt that sclerosing lesions represent a distinct, more aggressive variant of BCC possessing a greater malignant potential.

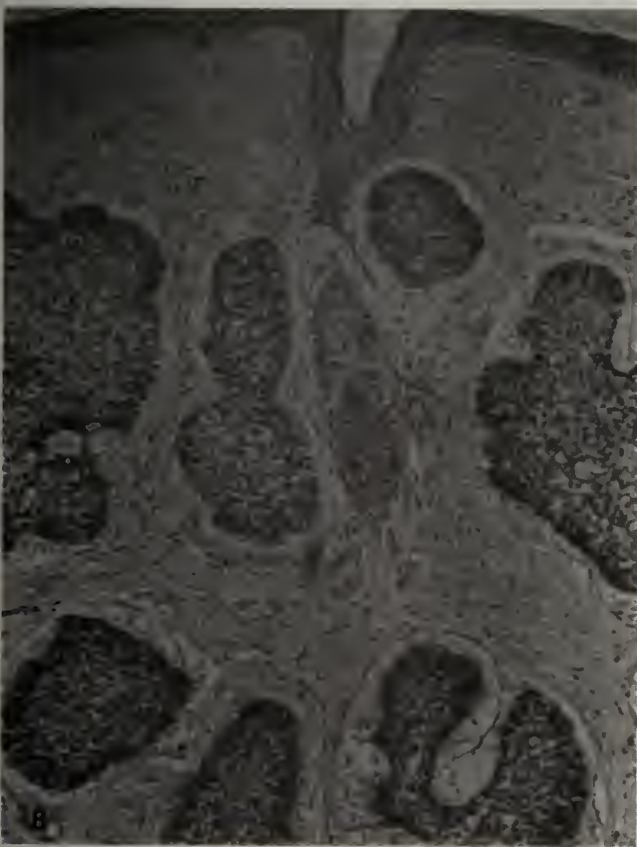


Figure 8. Classical histologic appearance of a basal cell carcinoma. (H & E stain, magnification X 400).

Treatment

Electrodesiccation and curettage. Electrodesiccation and curettage (EDC) is the most common method for treatment of basal cell carcinoma, favored by many practitioners. Cure rates as high as 96% to 100% have been reported,¹² but when size is the primary determinant, the overall cure rate is only 74%.³ In Dubin and Kopf's³ extensive review, tumors less than 2 mm in diameter were completely eradicated 100% of the time; lesions 2-

2-5 mm in size were excised *in toto* 85% of the time; and when larger than 3 cm, half of all tumors recurred, for a mere 50% cure rate. The authors³ caution that, while simple and mostly effective, EDC should be limited to the very small lesions.

Radiation. Radiation for the treatment of skin malignancies claims an overall cure rate of 92%,³ but requires specialized personnel and equipment and should be reserved for older individuals who are not surgical candidates, because the resultant scar tends to become worse, with time (20-30 years) and may even ulcerate. Despite a small risk of radiation osteitis and chondritis in certain areas, this is a safe, noninvasive method in selected patients.

Surgery. Surgical excision is the time-honored method of choice in skin cancer, with cure rates ranging from 85% to 95%.¹³

Dubin and Kopf obtained a 91% overall cure by surgical excision, with the success rate decreasing as size of the lesion increased. They also noted the importance of the anatomical location of the tumor: on the neck, trunk, limbs, or genitalia, the cure rate was 98.5%, whereas in the ears, eyes, and scalp, only 75-80% of lesions were cured. Their data agree with those of Shanoff et al,¹⁴ who found certain anatomical sites were singularly prone to recurrence of BCC.

One of the reasons for the high rate of recurrence in certain areas is obviously the lack of adequate margins during the resection. Some locations (e.g., the forehead) as well as some types of tumor (e.g., morphea-like or sclerosing) also show a propensity for large sub-clinical extension.

Micrographic surgery. The technique of micrographic surgery was developed by Frederick Mohs¹⁵ in 1932. Originally it was called "chemo-surgery" because it combined zinc chloride as a fixative and microscopic control of surgical excision. It did not receive popular acceptance until 1970, when Tromovitch¹⁶ presented his results with the fresh-tissue modification, which does not involve a chemical fixative.

Briefly, Mohs micrographic surgery as it is performed today consists of excising the visible and palpable tumor in saucerlike layers while drawing a map of the lesion that exactly duplicates its size and shape. Horizontal frozen sections of the entire undersurface of the excised tissue are made and examined microscopically. Wherever tumor is found, this is duly marked on the "map" and localized for further resection. The process is repeated until all tumor is removed.¹⁷

Cure rates by the micrographic technique are 99% for primary BCC and 96% for recurrent BCC. Mohs achieved 94% cure in primary SQC¹⁸ and 84% when treating recurrent SQC.¹⁹

Surgical Margins

Most standard texts recommend lateral margins of 5 mm when excising a basal cell carcinoma. Epstein²⁰ found that visual assessment of the margins of a BCC was within 1 mm in 94% of cases, and concluded that a 2-mm margin gave a 94% cure rate in small nodular lesions, but

sharply declined with larger tumors or those of the fibrosing or morphea-like type.

Squamous Cell Carcinoma

Squamous cell carcinomas usually begin as nodules that proceed to ulcerate (Figs. 9, 10, 11 & 12). Squamous cell tumors tend to be more inflammatory, feel more indurated, grow more rapidly, and ulcerate much sooner than BCC. Surface appearance may be smooth, verrucous, papillomatous, or ulcerative.



Figures 9, 10, 11 and 12. A 71 y/o male patient who presented with an ulcerated squamous cell carcinoma of the skin of the cheek.

"En-block" excision of the lesion with superficial parotidectomy was performed and the defect was reconstructed with a cervical flap.

Squamous cell cancers of the skin are only one-fourth as common as basal cell carcinomas. Compared to BCC, cutaneous squamous cell carcinomas show an even stronger actinic correlation, as evidenced by a very high incidence in white-skinned individuals and a decided preference for the sun-exposed extremities, head, and neck. The risk for developing squamous cell cancer of the skin climbs proportionately with length of exposure to sunlight, and is cumulative with age.²¹

With the exception of carcinoma *in situ*, squamous cell tumors rarely arise from unaltered, normal skin. Some premalignant change is usually seen on careful examination, to include sun damage, actinic keratoses, leukoplakia, radiation keratoses or dermatitis, scars, chronic ulcers, or sinuses.²²

Histopathology

A nodular or ulcerative squamous cell carcinoma consists of irregular masses of squamous epithelium that proliferate downward to the dermis. (Figs. 13 and 14). The proportion of atypical pleomorphic and anaplastic cells varies with the grade of tumor, which is in turn deter-

mal cytokeratin antibody, which is specific for tumors of squamous epithelium, and the antibody to S-100 protein, which selectively stains melanocytes and Langerhans cells.²⁴

Treatment

Treatment of squamous cell carcinomas follows similar approaches as the ones discussed for basal cell carcinomas. Yet because of the more aggressive nature of the malignancy surgery has been more often used and margins of resection should often be examined by frozen section to prevent incomplete excisions.

Mimics of SQC

Keratoacanthoma. Keratoacanthoma was first described by Hutchinson in 1889.²⁵

Solitary keratoacanthoma is more common than the multiple type, and usually occurs on exposed parts such as the middle of the face, lips, and back of the hands. It typically arises as a firm, small half-moon covered by normal skin except for a central keratotic plug (Figs. 15 & 16).



Figures 13 and 14. A patient with a squamous cell carcinoma of the forehead and the classical histologic appearance.
(H & E stain, magnification X 400)



Figures 15 and 16. Keratoacanthoma of arm and the histologic appearance.
(H & E stain, magnification X 400)

mined by changes in size and shape of the cells, hyperchromasia, keratinization, and the presence of mitotic figures. In the higher grades of tumor, cell differentiation and hence keratinization are greatly diminished, while mitoses are conspicuous and most cells are atypical, often spindle-shaped.

The degree of cellular differentiation is a significant predictor of tumor recurrence: 7% if well differentiated, 23% if moderately differentiated, and 28% if poorly differentiated. Depth of tumor invasion to a Clark IV of V level also increases the risk of recurrence/metastasis severalfold.²³

Some highly anaplastic skin tumors are impossible to categorize by light microscopy alone and must be carefully evaluated by immunohistochemical studies, for the diagnosis will determine the therapy to be given and expected clinical course. Immunoperoxidase stains can distinguish desmoplastic melanoma and poorly differentiated squamous cell carcinoma from other spindle cell tumors. Further differentiation is possible with epider-

Average size of a keratoacanthoma is 1 to 1.5 cm, but lesions up to 5 cm in diameter have been reported. The nodule grows rapidly for six to eight weeks, at which time it usually begins to disappear spontaneously. Resolution will continue for the next six to eight weeks until all tumor is resorbed and the corneal plug sloughs. According to this timetable, most lesions will have a lifecycle of four to six months, although a few may take nine months or more to run their course.²⁶

Some authors^{25, 27} recommend surgical excision of keratoacanthomas despite their benign nature because the scar that results from spontaneous resolution is often worse than if the lesion is excised.

Although definitely nonmalignant, the rapid growth of keratoacanthomas occasionally causes them to be mistaken for carcinomas. There is also the possibility of a highly anaplastic squamous cell carcinoma masquerading as a keratoacanthoma. Biopsy should extend from normal skin to normal skin through the center of the crater. To aid in the diagnosis, Kern and McCray²⁸ list ten histopathologic criteria to differentiate between keratoacanthomas and squamous cell carcinomas.

Pseudoepitheliomatous hyperplasia. This condition is caused by chronic inflammation secondary to fungal infections, draining sinuses, fistulas, and nonspecific ulcers. It is a proliferative process yet completely benign. It may be difficult to differentiate between pseudoepitheliomatous hyperplasia and a verrucous carcinoma.²⁹

An attempt has been made to review the usual clinical presentation and current management alternatives for the most common skin malignancies in Puerto Rico. The high incidence of these cancers in areas of high sun exposure like the Caribbean Islands makes it desirable that all physicians practicing in these geographic areas have a good working knowledge of their diagnosis for adequate referral and prompt management.

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CME REVIEW QUIZ

Please answer in the space provided in the registration form if the following statements are true (T) or false (F).

- Skin malignancies are not very common in Puerto Rico.
- Basal cell carcinomas account for 75-78% of the cutaneous malignancies.
- Ultraviolet radiation (UVB in particular) is responsible for much of the chronic sun damage and malignant degeneration occurring in human skin.
- Topical agents used as suncreeners fall into two major classes: the physical reflectors and the chemical absorbers.
- The so-called rodent ulcer is a form of squamous cell carcinoma.
- Acceptable forms of treatment for small basal cell carcinomas, include electrodesiccation & curettage, radiation and surgery.
- Squamous cell carcinomas are more aggressive than basal cell carcinomas.
- Actinic keratosis is a pre-malignant skin change resulting from chronic, cumulative sun exposure damage.
- The degree of cellular differentiation of squamous cell carcinomas is a significant predictor of tumor recurrence.
- Keratoacanthomas are often difficult to differentiate from squamous cell carcinomas.



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CLINICAL STUDIES

Stomach Cancer in a Native and Migrant Population in Puerto Rico and New York City, 1975 to 1979

Bárbara Menéndez-Bergad, PhD*
Steve Blum, PhD**

Puerto Ricans represent the second largest Hispanic group in the United States, after Mexicans. During the 1950's, an average of 41,000 Puerto Ricans migrated to the United States each year, but by the mid-1960's the migration flow was reversed.¹ The 1970 Census of Population revealed that 13% of the Puerto Rico population over 14 years of age had lived in the United States in 1965, indicating that reverse migration also occurs in sizeable numbers.²

Although Puerto Ricans are not a "typical" migrant population since they are United States citizens and travel frequently between the two countries without the restrictions experienced by other migrant groups, in many ways they are ideally suited for migrant studies. Because they are citizens, biases related to illegal residence and resulting population undercounts are minimized in relation to other migrants. The existence of tumor registries in Puerto Rico and New York make incidence and survival studies feasible.

Previous studies of cancer among Puerto Ricans have not analyzed survival and have mostly emphasized mortality.³⁻⁸ This study is the first to examine survival among Puerto Rican migrants and to use survival as a tool in interpreting changes in mortality.

Methods

Stomach cancer incidence data were provided by the New York State and the Puerto Rico tumor registries while mortality data were provided by the respective vital records offices. The Census Bureau provided intercensal estimates by age, sex, and place of birth for residents of New York City and Puerto Rico for the years 1975

through 1979.⁹ All incidence and mortality rates are based on five year annual averages per 100,000 population. The International Classification of Diseases for Oncology, codes 151.0 through 151.9, was used to identify stomach carcinoma.¹⁰ The chi square test statistic was used to determine whether or not there were significant differences in rates between migrants and sedentes by testing the proportion of persons with and without stomach cancer among the groups of interest.

Survival status was ascertained from information available in the tumor registries, by review of patients' medical records, and by matching the incident cases' names (Puerto Ricans commonly use two first names and two last names), social security numbers, and dates of death to death tapes from Puerto Rico and New York State for the period 1975 through 1982.

Incidence

An incident case in New York City (NYC/PR, n=281) was defined as a person born in Puerto Rico and residing in New York City at the time of diagnosis of a primary stomach cancer between 1975 and 1979. In Puerto Rico, an incident case (PR/PR, n=2066) was a person born on the island and residing there at the time of diagnosis during the same time period.

Incident stomach cancers were excluded from the study if they were: duplicate cases within the registry (17 in PR/PR, 6 in NYC/PR); lymphomas (26 in PR/PR, 0 in NYC/PR because the tumor registry does not include lymphomas under the rubric of stomach cancer); under 30 years of age (17 in PR/PR, 1 in NYC/PR); or diagnosed with carcinoma-in-situ (0 in PR/PR, 2 in NYC/PR). Cases with multiple primaries of the stomach were only represented once.

To determine whether there were any differences in the quality of the data between the Puerto Rico and New York State tumor registries, a survey of 35 New York City hospitals was undertaken that revealed an estimated 8% underreporting of stomach cancer incidences.¹¹ Puerto Rico's tumor registry is a member of the Surveillance, Epidemiology and End Results (SEER) Program which has an ongoing quality control system in existence, thus minimizing underreporting.

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There were 181 deaths among Puerto Rican-born residents of New York City with stomach cancer coded as the underlying cause on their death certificates, for the study period 1975-1979. In Puerto Rico, there were 1,780 such deaths during the same time period.

The underlying cause of death is determined differently in the United States and in Puerto Rico. In the United States, it is assigned by a nosologist, based on a review of all listed causes on the death certificate, while reports by relatives are acceptable in Puerto Rico in absence of other information. Mortality rates for Puerto Rico were calculated with and without deaths reported by relatives.

Survival analyses were performed on incident cases diagnosed between 1975 and 1977, with survival truncated (censored) on December 31, 1982, thus allowing for a minimum of five years of follow-up. Excluded from the survival analysis were cases for whom follow-up information regarding survival status was unavailable, which consisted of 3 males and 1 female in PR/PR, and 5 males and 7 females in NYC/PR. Due to the small number of survivors among the latter, males and females were analyzed together.

Results

Incidence and mortality data for the five year study period were used to generate average annual rates for comparative purposes. Age-adjusted incidence rates were slightly higher among NYC/PR males (58.94 per 100,000) and females (27.58) compared to PR/PR males (54.48) and females (25.73), as presented in Table I. These differences were not significant. Differences in rates between the two populations were greatest when only histologically confirmed cases were analyzed. Histologically confirmed cases consisted of laboratory verification of stomach cancer diagnoses.

Table I

Average Annual Age-Adjusted Stomach Cancer Incidence Rates Per 100,000 Population by Sex in PR/PR and NYC/PR, 1975-1979*

	ALL CASES			
	Males		Females	
	Rates	# Cases	Rates	# Cases
PR/PR	54.48	1355	25.73	711
NYC/PR	58.94	166	27.58	115

Histologically Confirmed Cases Only

	Males		Females	
	Rates	# Cases	Rates	# Cases
PR/PR	42.97	1073	18.27	518
NYC/PR	48.79	144	25.16	106

*Adjusted to the 1970 U.S. Standard Population.

As depicted in Table II, age adjusted stomach cancer mortality rates were higher among PR/PR males (46.36) compared to NYC/PR males (37.29), and PR/PR females (22.76) compared to NYC/PR females (17.84). These differences persisted for both sexes even when PR/PR stomach cancer deaths lacking medical confirmation were excluded from the analysis.

Table II

Average Annual Age-Adjusted Stomach Cancer Mortality Rates Per 100,000 Population by Sex in PR/PR and NYC/PR, 1975-1979*

Group	Males		Females	
	Rates	# Cases	Rates	# Cases
PR/PR	46.36	1153	22.76	627
PR/PR Medically Confirmed Stomach Cancer Deaths	40.37	1002	19.69	542
NYC/PR	37.29	109	17.84	72

*Adjusted to 1970 US Standard Population.

Among cases eligible for survival analyses, the distribution of the stage of disease at the time of diagnosis, shown in Table III, were similar for PR/PR and NYC/PRs: 18% and 15% localized, 69% and 72% regional or distant, and 13% unknown in both populations. The distinction between regional and distant stage of disease was found to be inaccurate, therefore these two groups were aggregated. Overall, survival was consistently higher among NYC/PRs after one (43% vs. 35%), three (20% vs. 14%), and five (11% vs. 9%) years, as indicated on Table IV. The most dramatic difference in observed survival between age groups occurred among those 30-44 after one year of follow-up as 28% of PR/PRs remained alive compared to 74% of NYC/PRs. Observed survival was also notably higher in the NYC/PR group for ages 75+ after one (48% vs. 36%) and three (28% vs. 14%) years, and age groups 45-54 after three (21% vs. 10%) and five (16% vs. 7%) years.

Table III

Percentage Distribution of Stage at Diagnosis of Stomach Cancer in PR/PR and NYC/PR, 1975-1977

Stage of Disease	PR/PR		NYC/PR	
	# Cases	%	# Cases	%
Localized	175	18.0	17	14.9
Reg. + Dist.	671	69.0	82	71.9
Unknown	126	13.0	15	13.2
Total	972	100.0	114	100.0

Table IV

Observed Survival for Stomach Cancer Cases by Age,
In PR/PRs and NYC/PRs, Among Cases Diagnosed Between
1975-1977

Age	SURVIVAL					
	PR/PR		NYC/PR		PR/PR	
	1 YEAR	3 YEARS	5 YEARS			
30-44	28.1	73.9	15.6	18.5	9.4	9.2
45-54	38.7	36.8	9.7	21.1	6.5	15.8
55-64	38.8	37.0	14.9	25.3	10.9	14.8
65-74	39.2	33.3	14.4	14.8	9.5	7.4
75+	35.7	48.3	13.5	27.6	8.0	6.9
For All Ages Combined	35.4	42.7	14.1	19.6	9.3	10.7

Discussion

Previous migrant studies have indicated that immigrants to the United States who originated in countries at high risk for stomach cancer experience reductions in incidence and mortality rates in their new environment.¹²⁻¹⁵ Even though Puerto Rican migrants to New York City moved from a country at high risk for stomach cancer to one at low risk,¹⁶ they experienced increases rather than reductions in incidence rates.¹⁷

Several factors could have contributed to this unexpected outcome. Since Puerto Rico is part of the SEER program, it is unlikely that major underreporting of incident cases posed a problem, but if significant underreporting did occur, it would account for the higher incidence rates among NYC/PR. In addition, census undercounts could have resulted in higher incidence rates among migrants, but had that occurred, mortality rates should have been equally affected, and they were not. Furthermore it is also possible that migrants differed from sedentes, perhaps in social class or in other factors associated with the incidence of stomach cancer, and this difference was related to an increased risk of developing stomach cancer. In fact, we have estimated considerable under-reporting in NYC, which would result in even higher than reported incidence rates among NYC/PRs. Finally, another possible explanation is that migration did not lessen exposure to risk factors, most likely dietary in nature, associated with the development of stomach cancer, but instead these factors remained present or enhanced in the migrants' New York City environment. There is no evidence indicating that Puerto Ricans alter their diet when they migrate to New York City, especially in view of easy availability of Puerto Rican foods and cuisine.

More difficult to understand are the higher stomach cancer mortality rates among PR/PR in view of the higher incidence rates among NYC/PR. Under-reporting of stomach cancer as the underlying cause of death on New York City death certificates would account for lower mortality among NYC/PRs, as would over-reporting in Puerto Rico. Furthermore, if differences in mortality rates between NYC/PRs and PR/PRs are not artifactual in nature, one would expect higher survival rates among NYC/PR, which was indeed the case.

Two factors probably contributed to improved survival among migrants. The first, speculative in nature, suggests that treatment for stomach cancer is more successful in New York City than in Puerto Rico. The second, based on the fact that migrants developing stomach cancer were younger than sedentes, results in a higher probability of survival among the former since mortality is a function of age.

Limitations of this study include the lack of information on the frequency of travel between Puerto Rico and New York City as well as on the length of residence for Puerto Ricans in New York City. Consequently, length of stay in New York City could not be correlated to the development of stomach cancer, nor could a residence duration-response be established. An additional limitation is that observed survival does not take into account other causes of death, therefore survivors dying from any cause were classified as dying from stomach cancer.

Future studies which examine stomach cancer incidence, mortality, and survival among Puerto Ricans in New York City should investigate length of residence and changes in dietary patterns among migrants which may be associated with the development of disease.

Abstract: This study compares age-adjusted stomach cancer incidence and mortality rates, by sex, among Puerto Rican-born residents of New York City (NYC/PR) and Puerto Rico (PR/PR) for the time period 1975 through 1979. One, three, and five year observed survival for cases diagnosed between 1975 and 1977 were compared. The results indicate that age-adjusted stomach cancer incidence rates per 100,000 among NYC/PR males (58.94) and females (27.58) were slightly higher compared to rates among PR/PR males (54.48) and females (25.73), while age-adjusted mortality rates were substantially higher among PR/PR males (46.38 vs. 37.29) and females (22.76 vs. 17.84), although these differences were not statistically significant. Differentials in observed survival consistently favored NYC/PR after one (43% vs. 35%), three (20% vs. 14%), and five years (11% vs. 9%) of follow-up.

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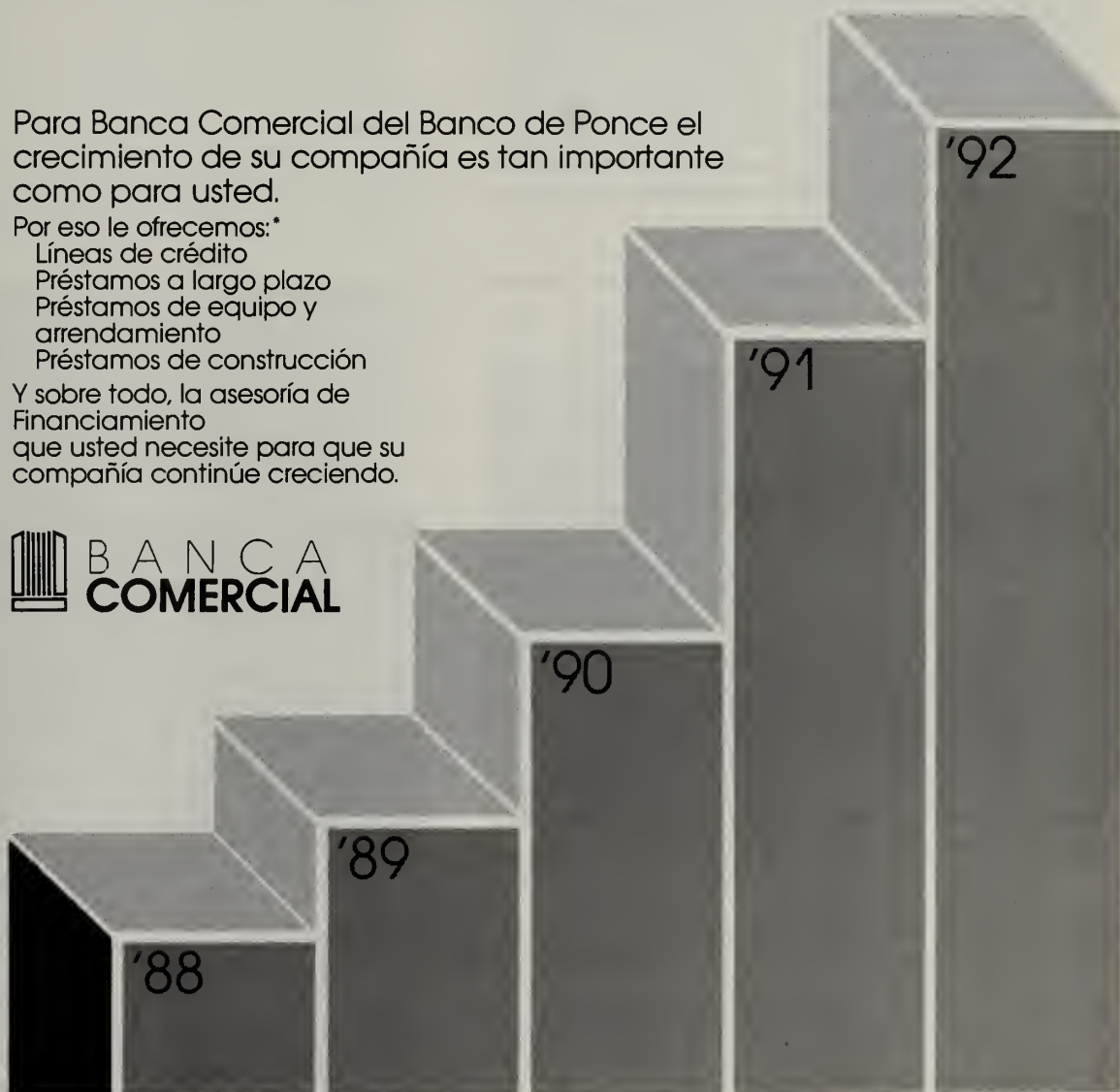
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Acute Histoplasmosis: A Modern Appraisal

José Ramírez Rivera, MD, FACP, FCCP*

Abstract: Acute histoplasmosis is an infrequently recognized pulmonary disease endemic in Puerto Rico. Two cases of acute histoplasmosis which followed an exposure to bat guano in a tunnel are presented. Negative cultures of bronchial washings and negative transbronchial biopsies illustrate the usual difficulty in establishing a definitive diagnosis. Serial serum complement fixation titers suggested a recent infection. The illness was quickly and effectively controlled with oral ketoconazole. When symptoms of acute histoplasmosis persist beyond two weeks treatment with ketoconazole for at least two months should be considered.

Histoplasmosis is a systemic granulomatous infection with a world-wide distribution. The infectious agent is the airborne spore of *Histoplasma capsulatum*, a fungus which, at warm temperatures, grows luxuriantly in mixtures of soil and decaying excrements of birds and bats. In the open air, temperatures of 68 to 90°F (22 to 29°C) and a relative humidity of 67 to 87 percent are associated with the highest rates of histoplasmin skin test positivity in the population and the most frequent isolation of the fungus from the soil.¹

In about 60 percent of the cases the infection may be asymptomatic; in 25 to 35 percent an influenza-like illness may be noted. Thus, in 85 to 95 percent of the infections symptoms are so few or nonspecific that the diagnosis is not suspected. The infection by *H. capsulatum* is identified months or years later when multiple calcifications are noted in the chest film or if there is a positive histoplasmin skin test.

It is estimated that in the United States 40 million people have had the disease and that there are 200 thousand new cases a year. In Puerto Rico the disease has been generally associated to exposure to decaying bat guano in caves.² The fungus was first recovered from the soil in 1964 from las Cuevas de los Panes in Utuado.³ Based on histoplasmosis skin tests island-wide, Sifontes estimates the prevalence of infection at 25 percent.⁴ In 1964 32.6 percent of the medical students in the University of Puerto Rico School of Medicine had a positive skin test.

To prevent histoplasmosis, the specific microenvironment where it may be acquired must be identified. The development of effective oral antifungal agents, and the new awareness that the acquired immunodeficiency syndrome is a risk factor for disseminated disease, calls

for a review of diagnostic and therapeutic strategies.

In this paper we present two men who developed progressive pulmonary histoplasmosis shortly after accompanying an engineer in the review of the structural conditions of a dark and humid tunnel populated by bats. Prompt treatment with oral ketoconazole cut short the clinical evolution of the illness.

Case 1

A 37-year-old maintenance worker developed fever, general muscle aches and cough in the middle of June 1988. He had visited a tunnel populated by bats a week earlier on an engineering survey. One month after the onset of symptoms, general malaise, low grade afternoon fever and dry coughing spells persisted. He had lost 17 pounds and had been unable to return to work. These symptoms, and the presence of diffuse nodular pulmonary densities 3-5 mm in diameter, led to hospitalization from July 14, 1988 to July 16, 1988 with the suspicion of pulmonary histoplasmosis (Figure 1).



Figure 1. Case 1- Chest film dated July 6, 1988 showing diffuse nodular pulmonary densities more marked at the bases.

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On admission the temperature was 36.8, pulse 86, respiratory rate 22, blood pressure 110/80. There was no adenopathy. The lungs were clear. Neither the liver or spleen were palpable. In the 48 hour hospitalization an 8:00 p.m. temperature of 38.5°C and a 9:00 a.m. temperature of 38°C were recorded.

Pulmonary function tests showed a mild restrictive and diffusion defect. A transbronchial biopsy yielded normal bronchial alveolar tissue. Bronchial washings failed to grow fungi. The patient was initiated in ketoconazole 400 mg daily. Within ten days fever abated and generalized symptoms resolved. His appetite improved and he gained 10 pounds in a month: after 2 months ketoconazole was stopped. When reevaluated 3 months after the infection he was asymptomatic; extensive resolution of pulmonary nodules had occurred (Figure 2). Complement fixation titers for histoplasmosis suggested recent infection (Table 1). Radiographic resolution has continued. A serum test for human immunodeficiency virus on October 4, 1988 was non-reactive.



Figure 2. Case 1- Chest film dated August 10, 1988 showing extensive resolution of pulmonary infiltrates.

Case 2

A 32-year-old conservation employee was exposed to bat guano in a tunnel on June 10, 1988. Fever and general malaise developed one week later. He was hospitalized from July 17 to July 19, 1988 for a diagnostic bronchoscopy because of recurrent fever, cough, myalgias,

headache, a loss of 15 pounds and nodular pulmonary infiltrates at the bases (Figures 3). Titers for histoplasma antibodies obtained three weeks after the infection were non diagnostic (Table 1). Bronchial washings were eventually negative for histoplasmosis on culture and a transbronchial pulmonary biopsy showed no granulomata.

Table 1

Serum Complement Fixation Tests for Histoplasmosis -1988				
Date	Case 1 Phase		Case 2 Phase	
	Mycelial	Yeast	Mycelial	Yeast
Jun 30	1:8	1:8	1:8	1:8
Aug 17			1:8	1:32
Oct 04	1:8	1:16	1:8	1:16
Nov 01	1:8	1:32	1:16	1:16



Figure 3. Case 2- Film dated July 29, 1988 showing scattered nodular infiltrates more prominent at the bases.

On admission the temperature was 37°C, pulse 84, respiratory rate 20 and blood pressure 130/90 mm Hg. There was no adenopathy no mouth thrush; neither the liver or spleen were palpable.

The patient was initiated on ketoconazole 400 mg daily and within one week the fever had disappeared and constitutional symptoms had improved. A mycelial phase complement fixation titer for histoplasmosis on August 17 was strongly suggestive of recent infection (Table 1). Ketoconazole was stopped after two months of treatment.

On September 8, three months after the infection, he was completely asymptomatic. He had a normal spirometric study. A chest film one month later showed almost complete resolution of the nodular infiltrates (Figure 4). A serum test for human immunodeficiency virus on October 4, 1988 was non-reactive.



Figure 4. Case 2- Chest film dated August 19, 1988 showing substantial resolution of infiltrates.

Discussion

The incubation period of histoplasmosis depends on the immune state of the infected person. Previously infected persons usually become symptomatic three to nine days after infection. Those not previously infected generally develop symptoms nine to seventeen days after infection.¹ The two patients presented here developed symptoms within a week of exposure; they fit the short incubation pattern seen in endemic areas for immunocompetent previously infected individuals.

Until recently it was thought that reinfection histoplasmosis occurred almost exclusively through the recurrent exposure to the offending spore; recurrent disease was thought to arise quite differently from reinfection tuberculosis. Experience with patients suffering from the acquired immunodeficiency syndrome suggests otherwise. In a recent study active or disseminated histoplasmosis has been demonstrated in immunocompromised individuals born in endemic areas but living in New York City, a nonendemic setting. Seventeen out of 18 patients were hispanic, thirteen were born in Puerto Rico. It is thought that these patients reactivated a latent infection when they became immunocompromised. This is excellent evidence that the yeast phase *H. Capsulatum* may not be eradicated after a first infection in untreated individuals. The fungus may remain simply under biological restraints until the hosts become immunocompromised.

As these two cases demonstrate, the definitive diagnosis of pulmonary histoplasmosis is frequently difficult in the immunocompetent. In the absence of cavitary disease Wheat et al could not obtain a single positive culture from bronchial washings in 35 cases and only three of fourteen transbronchial pulmonary biopsies were informative. In the immunocompromised the story is quite different:⁵ cultures of the bronchoalveolar lavage are positive in 69 percent of cases (9 of 13) and the transbronchial biopsy is diagnostic in the same number. In the

immunocompetent the most rapid and reliable way of arriving at a functioning diagnosis is to demonstrate a rising titer in the yeast phase of the complement fixation test, but only 16 percent of cases achieve the ideal four-fold increase. Titers of 1:8 and 1:16 are considered presumptive evidence of recent infection and titers of 1:32 are highly suggestive. Unfortunately, low grade titers are frequently observed in endemic areas in the absence of disease and titers may remain less than 1:8, non diagnostic, in 15 percent of cases of clinically convincing cases.⁶

Histoplasmosis skin testing is clinically not useful. It is strictly an epidemiologic tool; it does not differentiate current from past infections. Moreover, ten percent of patients with previously documented histoplasmosis may have a negative skin test.

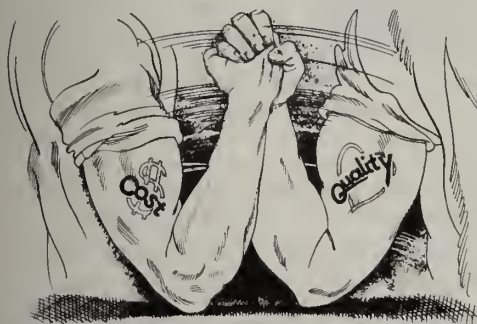
In general, symptomatic histoplasmosis is a self-limited illness requiring no specific treatment. When cough and fever persist for two or three weeks or the disease is radiographically progressive the possibility of dissemination rises.¹ Until recently the standard treatment was intravenous amphotericin. Because amphotericin has many side effects, and the intravenous treatment for two to six weeks is cumbersome and costly there has been a tendency to withhold treatment unless there was respiratory impairment or signs of dissemination. The advent of oral, less toxic, ketoconazole makes prompt treatment possible in moderately severe disease. Also, the new awareness that untreated histoplasmosis may remain as a clinically insignificant infection, only to disseminate when an immune defect develops, encourages dispensing antifungal treatment more generously.⁵

The appropriate dose of ketoconazole for the treatment of mild to moderate acute histoplasmosis has not been clearly established. For patients with severe progressive, chronic or disseminated disease a minimum of six months of treatment is indicated.⁷ A drop in the complement fixation titers and the demonstration of negative Gallium scans may be helpful in defining the treatment end point.⁸ The experience with these two patients suggests that 400 mg of ketoconazole daily for two months may be adequate treatment for mild to moderate progressive pulmonary disease.

Resumen: La histoplasmosis aguda es una enfermedad pulmonar endémica en Puerto Rico que se identifica con poca frecuencia. Se presentan dos casos de histoplasmosis aguda que se desarrollaron después de una exposición al excremento de murciélago en un túnel. Los cultivos negativos de los lavados broncoalveolares y la biopsia transbronquial negativa ilustran cuan difícil es establecer un diagnóstico definitivo de esta enfermedad. Los títulos seriados de fijación de complemento sugieren una infección reciente. La enfermedad se controló rápida y eficientemente con ketoconazole oral. Cuando los síntomas de histoplasmosis aguda persisten más de dos semanas el tratamiento con ketoconazole por un mínimo de dos meses debe considerarse.

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SPECIAL ARTICLES

Ethics and Bioethics*

Herman J. Flax, MD, FACP**

Summary: The Biomedical Ethics Advisory Committee is not concerned with infractions of the hospital's by-laws or the personal, professional code of ethics of the physician. It answers consultations relative to moral issues involved in possible infractions of patients' rights. As much, after studying the moral issues involved, the committee presents the referring physician with advice that will enable him to render a valid decision in accord with preservation of the patient's rights and avoidance of possible future legal involvement.

Biomedical ethics is the employment of a set of moral rules by the physician in the practice of medicine. It is a measure to gage the moral code of conduct between physician and patient. It can provide a modern version of the ancient oath of Hippocrates that has governed the practice of medicine for the past 2000 years.

Yet, the interpretation of a moral code or a set of rules to govern medical practice is not as simple as it sounds. Our laws says, you shall not kill. Yet, recently, I saw a television documentary from Holland stating that 20 percent of the deaths there in 1987 were due to euthanasia, death by physicians. Of course, this was done legally at the request of the patient, who had prepared a valid living will while competent. So, can we say, "Euthanasia is an ethical way to die?" Or better still, "Euthanasia is a moral practice of medical ethics?" Many argue that euthanasia is morally unacceptable.¹ In Puerto Rico, as well as everywhere else in the civilized world, a physician, who sends terminal patients to glory painlessly instead of letting them spend their last days in agony, will be accused of murder by the District Attorney. What is moral blessing in Holland is moral turpitude in the rest of the civilized world.

Moral values and moral codes are generally possessed with philosophical interpretations. Ethics has been defined by Webster² as moral philosophy. He also states

that morals are the "principles and practice in regard to right, wrong, and duty." Certainly, all physicians understand these principles. We may not all be philosophers; but, because we are professionals, we are practitioners of ethics.

My presentation will not be directed to professional ethics but to biomedical ethics. There is a difference which may not be clear in the minds of many physicians. Although important, I will not discuss adherence to hospital by-laws and rules, conformity with the Joint Commission on Accreditation of Hospitals (JCAH) standards, questions of physician's competence, or quality assurance procedures that analyze patient care. I will be concerned with the importance of respecting patient's autonomy in resolving ethical dilemmas.

The patient must be given the opportunity to participate in decisions relative to his/her health. If the patient is incompetent, then the legal channels of family and, finally, the court must prevail. Patients have the right to govern their own persons, are responsible for own activities, have a right to know, to be told concerning and a right to reject treatment. The physician must respect the patient or family's ability to make these decisions. The physician can no longer assume a paternalistic attitude, must keep the patient well-informed of the procedures used in treatment, and, above all, must not lie to the patient. Shulman³ summarized this very well: "The true role of the physician is not to make paternalistic decisions on behalf of the patient but to enable that patient to make a decision on his or her own."

In between, of course, there are many moral dilemmas, and this is why the hospital seeks the advice of the Biomedical Ethics Advisory Committee (EAC). It is not the function of this committee to restore patients' rights; it is the duty of the committee to prevent the abuse of these rights by the medical staff. In this way, the committee attempts to protect the hospital against probable malpractice claims. The EAC, as the name implies, is an advisory group. It does not decide, nor should it be made responsible to decide, the precipitating ethical problems. The decision is still the province of the physician. Nor, is it the duty of the committee to dictate the practice of medicine. This is the dominion of the physician. However, the EAC does defend the individual rights of patients.

*Presented in Seminar on Medical Ethics, Puerto Rico Medical Association, November 16, 1988

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Before presenting a few examples, I would like to discuss three fundamental ethical dilemmas: 1) Informed consent, 2) Right to die and 3) Paternalism. Although, there may be other ethical problems brought before the EAC, most of the consultations concern these three.

A valid consent is an informed consent. First, the physician must give the patient adequate information about all alternatives to treatment including no treatment. The physician must discuss the benefits and all the risk in simple language, and the patient must understand what is explained. Second, there must be no coercion. Patients have a rights to refuse medical and/or surgical procedures, and they cannot be forced to accept same against their will. Thirdly, the patient must be competent. A competent patient understands and appreciates information. The patient who consents but doesn't understand the risks is not capable of making an acceptable decision. Neither can the unconscious nor the mentally deteriorated patient. They are incompetent and are unable to make a valid consent, because they cannot express their wishes rationally and because they do not understand what the physician is proposing.

A person has a right to express his/her desires as regards management of dying. Unfortunately, few people leave a living will or a power of attorney outlining desires formulated while alive and competent. If they do, these wishes must be respected. A competent patient can refuse to allow procedures to prolong life. Problems arise when the patient is unconscious or incompetent. It may be possible that the patient has previously discussed his/her desires with the family. If so, they should comply with the patient's requests. However, the physician should understand the legal procedures that must be followed in the local community. In Puerto Rico, the law does not permit discontinuation of treatment from a dying person, once started, unless the court gives permission. This is also true about stopping food, water, medication and other life-support systems from a patient in the vegetative state.

We have already alluded to paternalism. Regardless of what the physician thinks is best, he cannot and should not enforce his will without the consent of the patient. The physician must explain all procedures and must pursue the patient's rational desires. If he doesn't, he may have to explain his reasons in court.

A previous paper,⁴ published in the "Boletín de la Asociación Médica", explains the organization and work of the Biomedical Ethics Advisory Committee of the San Juan VA Medical Center. This committee is composed of eleven members from the medical and allied health professions, the chaplain, district counsel and a lay representative. It has accumulated three years of experience in providing advice on ethical dilemmas that have confronted the hospital staff. From this experience we can state that the committee members must have a working knowledge, indeed, be educated and gifted in the following: 1. Be able to identify the moral aspects of medical care if and when there is a dilemma or grievance. 2. Ability to know how to obtain a valid consent or refusal. 3. Know how to proceed when a patient is only partially competent. 4. Must understand the role of the guardian or next of kin; know when to go to court to appoint a guardian; understand the function of a

surrogate. 5. Knowledge of how to proceed if the patient refuses treatment; criteria to treat an unwilling patient. 6. Decide when it is morally justifiable to withhold information; justifiable paternalism. 7. Decide when it is morally justified to breach confidentiality; i.e. about A.I.D.S. patient. 8. Knowledge of moral aspects of terminal care; when to eliminate life-support treatment. 9. Awareness of the role of advanced "Do Not Resuscitate" (D.N.R.) directives; withholding food and water. 10. Knowledge of relevant local laws, policy about living wills and power of attorney.

Three recent consultations from the files of the San Juan VAMC Biomedical Ethics Advisory Committee will be presented to illustrate practical solutions to moral dilemmas that arise in the hospital setting.

Patient 1 was referred by the Chief of Staff. The patient, a Jehovah's Witness, has kidney failure, treated by peritoneal dialysis. Now, he has a severe anemia and the Medicine Service ordered blood transfusions. The patient, despite all indications, refused the transfusions, because this is against his religious beliefs. His wife also a practicing Jehovah's Witness, does not wish the patient to be transfused. They do not have any children. The Medicine service insists on the blood transfusion and requested that the District Counsel seek a court order obligating the patient to accept this treatment.

The EAC understands that the patient is competent and has repeatedly refused to receive blood transfusions because of his religious beliefs. Although Jehovah's Witnesses do not accept blood transfusions, they welcome alternative treatments that will keep them alive. The EAC made the following recommendations: 1) The decision of the patient must be accepted, because he is competent. 2) There should be a note in the patient's record stating that he has refused constantly to receive blood because of his religious beliefs and that his wife also refuses. 3) The note should state that all alternatives have been explained to the patient, that he understands the consequences of not receiving blood, and is mentally able to make a decision; and 4) the patient should sign the regular form, refusing treatment.

This case illustrates two of the classical dilemmas: Paternalism and Informed Consent. Paternalism in so far as the Medical service insisting on the blood transfusion regardless of the patient's desires, and trying to override the refusal of the patient to give his consent by means of a court order. It is hardly likely that a judge would force the patient to receive the blood transfusion against his will since there was no doubt about his competency. Competent patients are in complete control of their bodies, and no one can force their acceptance of any therapeutic measure against their will.

Patient 2 was referred by the Medical service because he went into renal failure and developed uremia. He refused dialysis. The attendant physician considered the man to be alert and oriented at the time but was worried that the family would not authorize dialysis once the patient went into coma.

The EAC answered the consultation as follows: The patients if he is rational, has a perfect right to refuse dialysis and cannot be forced to undergo this treatment against his will. Not even when the patient becomes

incompetent can the family agree to dialysis, because he has expressed his will, while mentally competent, that he does not want this treatment.

The EAC suggested that the physician explain the alternatives, although for this patient there really are none. The physician must tell the patient and the family that he will die unless dialysis is instituted. He must also tell the family that they cannot go against the will of the patient, even when he becomes comatose. The physicians was advised to get a psychiatric consultation if there was any doubt about competency. The patient should sign and the signature be witnessed that he refuses dialysis. If no other treatment is necessary in the hospital, the patient should be discharged home.

The dilemma, here, was the desire on the part of the attending physician to get the family's consent to dialysis after the patient would become incompetent because of the complications following the renal shut-down. Although the physician considered the patient competent at present, he would become incompetent later. The physician knew that the patient would die without dialysis, so he was looking for a way to save the patient's life, utilizing a treatment the patient does not desire.

A determination of the mental state by a psychiatrist is in order, because legally, only the psychiatrist can make a valid determination of competency. Although the patient did not leave a valid "living" will, he did express to the physician and to the family several times that he did not want this treatment. This desire must be respected even when the patient becomes incompetent. Simply stated, a competent patient has a right to refuse treatment even if it kills him. How much easier it would be if everybody left a "living" will specifying exactly what we desire with our persons when we become incompetent.

Patient 3 is a middle-aged veteran who tested positive for HTL VIII virus, AIDS. He refused to permit the attending physician to inform his wife of this result. The EAC was consulted for advice.

There was a big discussion concerning the release of confidential information without the expressed consent of the patient. AIDS is not yet included in the obligatory reporting of transmittable diseases in Puerto Rico. All the members of the committee decided that it was important to protect the wife by informing her of the necessary precautions she must take while living with her husband. This includes prevention of contact with all secretions, not only semen during intercourse but saliva, blood, and body wastes. The VA has determined the VA physician should make reasonable efforts to counsel and encourage the HIV positive patient to provide such information to the spouse or sexual partner.⁵ If the patient will not do so, and the attending physician reasonably believes that he will not, then the physician will make this disclosure in order to protect the health of the spouse.

As a result of the Tarasoff⁶ ruling by the Supreme Court of California in 1976, The Codes of Ethics of the American Psychiatric Association and the American Medical Association allow their members to divulge confidences if the safety of the community is at stake. There are other legally required government reporting that abolish confidentiality. These include gun-shot wounds, child abuse, elderly abuse, venereal and certain infectious

diseases. The patient should be informed that these reports are required by law, but non-reportable information is held strictly confidential.

Conclusion

There are, of course, many other ethical dilemmas that confront the hospital staff. The more important involve decisions to forego life-sustaining treatments in terminal patients, such as "do-not resuscitate" (DNR), withholding water, food and medication. Other moral issues concern religious beliefs, as abortion, sterilization and circumcision. Still another group is found in competent but handicapped patients who wish medical treatment terminated against their physician's advice. In arriving at a practical conclusion in all these referrals, the EAC must not only have the best interest of the patient at heart, but must also have a clear understanding of the laws of the land. There are legal restrictions to resolving moral dilemmas and these supercede all ethical decisions by the committee.

Resumen: El Comité Asesor de Ética Biomédica no vela por infracciones a los reglamentos del hospital o los códigos de ética personal o profesional del médico. Este responde a consultas relacionadas con asuntos morales que envuelven posibles infracciones a los derechos del paciente. Luego de estudiar el asunto moral envuelto, el Comité le presenta al médico que consulta ciertas recomendaciones que le permiten a éste tomar una decisión aceptable en acorde con la preservación de los derechos del paciente, tratando de evitar posibles problemas legales en el futuro.

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Mirada a Nuestro Pasado - Hace 50 Años...

Introducción al Estudio de las Enfermedades Cardiovasculares en Puerto Rico

A. Fernos Isern, MD*

Las enfermedades del corazón aparecen como la séptima causa de muerte, en orden de magnitud, en Puerto Rico, de acuerdo con la clasificación internacional de causas de muerte. Esta clasificación divide la diarrea y enteritis en dos renglones: uno para los menores de dos años y otro para los mayores de dos años. Uniendo ambos renglones en una sola denominación, las enfermedades del corazón ocuparían en realidad la sexta causa de muerte.

Por razones etiológicas y lógicas, entidades tan respetables como la Metropolitan Life Insurance Co., estudian las enfermedades del corazón y las enfermedades renales en un solo renglón, titulado, Enfermedades Cardiovasculares y Renales, grupo que vendría a ser en Puerto Rico el 3, entre las principales causas de muerte dejando atrás a la malaria y a la pulmonía. El orden entonces sería el siguiente: 1. Diarrea y enteritis para todas las edades; 2. Tuberculosis; 3. Enfermedades cardiovasculares y renales; 4. Malaria y 5. Pneumonía. Seguirían después enfermedades del puerperio, cáncer, uncinariasis, sífilis, accidentes, suicidios, influenza y bronquitis en proporción variable, pero en número proporcionalmente menor. De modo pues que aun agrupando las enfermedades renales con las cardio-vasculares, vendrían como hemos dicho a ocupar un tercer lugar en Puerto Rico; separándolas, las enfermedades del corazón ocupan solo un sexto o séptimo lugar; mientras que en Estados Unidos, las enfermedades del corazón por sí solas son la principal causa de muerte y con más razón si se les agregan las renales.

Ahora bien, las enfermedades del corazón, tienen fundamentalmente dos causas etiológicas principales: 1. una es, la de las condiciones infecciosas (incluyendo de modo general y principal entre ellas las afecciones reumáticas y las sífilíticas); otra las enfermedades, 2. degenerativas, que aparecen por lo general después de los 40 años.

Las afecciones infecciosas con repercusiones cardiovasculares (condiciones reumáticas y sífilis) son propias o de la niñez (reumáticas) o de las edades jóvenes y medianas (reumáticas y sífilíticas). Las afecciones degenerativas son generalmente propias de edades mayores.

Una población más vieja como es la de Estados Unidos respecto de la de Puerto Rico tiene que ofrecer una incidencia mucho mayor de enfermedades cardio-vasculares degenerativas que una población joven como la nuestra. Pero como además las afecciones reumáticas son mucho más frecuentes en Estados Unidos que en Puerto Rico es lógico que este factor también influya en una incidencia mucho más baja por enfermedades del corazón en Puerto Rico que en Estados Unidos; en otras palabras mientras en Estados Unidos la niñez está siendo atacada por las afecciones reumáticas, la juventud y la madurez por afecciones sífilíticas; la madurez y vejez (numerosas) por condiciones degenerativas, en Puerto Rico la niñez está siendo atacada mucho menos por el reuma, la juventud y la madurez al igual por la sífilis; la edad madura y la vejez, por ser menos numerosas, contribuyen con menor número de óbitos a la mortalidad por enfermedades degenerativas. Así se explica que en 1939, la mortalidad en Estados Unidos por enfermedades del corazón fuera de 184.3 por 100,000 mientras en Puerto Rico lo fuera solamente de 107.2 por 100,000. Paradójicamente, pudiera decirse que esta baja mortalidad por enfermedades del corazón en Puerto Rico no significa mayor salud en nuestra población, sino peor salud; significa en parte que no hay un suficiente número de personas que vivan lo bastante para llegar a la edad de las enfermedades degenerativas y que pudieran robustecer el coeficiente de mortalidad con dichas enfermedades, apesar de no estar acechadas en la niñez, por las afecciones reumáticas.

A este respecto las cifras del Dr. Koppisch, a base de autopsias realizadas en la Escuela de Medicina Tropical, son muy elocuentes. El Dr. Koppisch nos informa que en 639 autopsias verificadas hasta 1933, 7 presentaban procesos reumáticos activos o sea 1.109%. Pero la impresión de Koppisch, desde un punto de vista patológico, y que coincide con la mía personal a base de observaciones clínicas, es que el proceso reumático en Puerto Rico es menos agudo, es menos activo, es en fin menos grave que en Estados Unidos.

Otra impresión personal de Koppisch, por cierto, muy interesante, es de que la arterioesclerosis entre nosotros aparece a edades más tardías o mejor dicho que espera a presentarse abundantemente aquí allá para los 58 y 60 años de edad, mientras que en Estados Unidos abunda desde los 40 años en adelante. Esto dejaría la sífilis en

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posición relativa de mayor importancia como causa de muerte en las edades entre 30 y 60 años entre nosotros y así se podría explicar que mientras en Puerto Rico la sífilis ha producido el 26% de muertes repentinas, a base de autopsias en la Escuela de Medicina Tropical, la arterioesclerosis produjo el 14.7%. (Koppisch) En el Norte, según las estadísticas a la disposición, la arterioesclerosis produce el 30% de muertes repentinas y la sífilis solo de 10% a 12%. Esto no quiere decir que la sífilis sea más frecuente en Puerto Rico que en Estados Unidos, sino que se distingue más entre nosotros por la relativa infrecuencia de las otras causas.

En 900 autopsias, Koppisch, ha encontrado 76 casos con lesiones indubitables de sífilis a las que, agregando 27 sin lesiones, pero con historia serológica positiva, hacen un total de 103 sífilíticos o sea 11.4%, una incidencia análoga a la que se encuentra en Estados Unidos. Las lesiones halladas fueron 62 aortitis, 20 sin aneurisma, 42 con aneurisma, 10 con invasión de las válvulas aórticas y 7 con estenosis de las arterias coronarias. Sabido es que estas son las formas en que generalmente se presenta la sífilis cardio-vascular, ya que el goma sífilítico del miocardio es lesión sumamente rara y que lo es más la miocarditis intersticial sífilítica, condición que por otra parte se duda exista en realidad.

La mortalidad por enfermedades del corazón en Puerto Rico para 1936 fue de 114 por 100,000. Durante este año el 47.7% de estas muertes ocurrieron en la zona urbana y el 52.3% en la zona rural. Puesto que nuestra población es eminentemente rural (en un por ciento no menor de 75) es evidente que la mortalidad por enfermedades del corazón es 3 veces mayor en la zona urbana que en la rural. También la sífilis entre nosotros, según los estudios de Costa, y como es lógico, es enfermedad eminentemente urbana.

Durante ese mismo año de 1936 solo 44 personas murieron por enfermedades del corazón con edad menor de 35 años, entre 35 y 65 ocurrieron 76 muertes; de más de 65 ocurrieron 85.

Dado nuestro promedio de vida, tienen evidentemente importancia entre nosotros, las enfermedades del corazón entre mayores de 35 y menores de 65; la edad de la sífilis cardio-vascular y de las enfermedades degenerativas. En la primer mitad de este período o sea de 35 a 50 años, la principal causa de muerte por enfermedades del corazón es la sífilis, después de los 50 y hasta los 65 la arterioesclerosis y otras formas degenerativas. (Datos de informes oficiales). Desde un punto de vista de salud pública pues, y desde un punto de vista social, la sífilis cardio-vascular sería el sector principal a atacar en un esfuerzo por disminuir la mortalidad por enfermedades del corazón en Puerto Rico. Desde un punto de vista social, porque de los 35 a los 50 es indudablemente la edad socialmente más importante del hombre. Desde un punto de vista de salud pública porque mientras, ante las demás causas estamos prácticamente desarmados, ante la sífilis disponemos de armas efectivas y de conocimientos suficientes para evitar y combatir la enfermedad.

La sífilis aórtica se presenta en tres formas: (a) Una aortitis simple, que produce pocos síntomas y apenas produce signos físicos; (b) En casos más avanzados, aortitis con extensión a las válvulas aórticas; con insu-

ficiencia aórtica consiguiente, y (c) Con aneurisma, o ambas formas.

La insuficiencia del miocardio, el *Heart Failure*, sobreviene por uno de dos factores; o por insuficiencia de las válvulas aórticas, con hipertrofia del miocardio, o por injuria a las arterias coronarias en su arranque aórtico, resultando entonces insuficiente el riego sanguíneo del músculo cardíaco. Del tratamiento de las manifestaciones graves de la sífilis del sistema cardio-vascular dice Padge, de Baltimore, en "Modern Concepts of Cardio-vascular Disease", (octubre de 1936) que no es tan fútil como se pensaba en el pasado y que el tratamiento en las formas menos graves (aortitis sífilíticas sin complicaciones) puede ser brillante, pero la enfermedad cardio-vascular sífilítica, es una enfermedad más bien a ser prevenida que a ser tratada. La erradicación de la sífilis cardio-vascular, sigue diciendo Padge, depende del tratamiento adecuado de todos los pacientes con sífilis reciente, tanto porque al quedar así tratada esa persona no disemina la enfermedad, como porque las posibilidades de que desarrolle más tarde las formas cardio-vasculares quedan reducidas prácticamente a cero.

Y, aún cuando la aortitis se haya presentado, el tratamiento debe establecerse diligentemente, pero ya condicionándolo, teniendo en cuenta cinco principios cardinales, a saber 1. Para evitar la producción del choque terapéutico conocido por reacción de Herxheimer el tratamiento debe empezar por los metales pesados y los yoduros. 2. Para evitar la paradoja terapéutica o sea una cicatrización de lesiones muy rápidas con formación de cicatrices muy grandes, debe empezarse el tratamiento con los metales pesados y los yoduros. 3. Para evitar reacciones graves por el tratamiento, del tipo nitritoide, no debe usarse arsénamina en pacientes aparentemente muy enfermos. 4. Para evitar las reacciones de tratamiento de carácter menor de tipo nitritoide, deben aplicarse los arsenicales en dosis pequeñas. 5. Para conseguir los efectos máximos el tratamiento debe ser continuo y prolongarse hasta no menos de dos años, debiéndose alternar los cursos de Bismuto con los cursos de neoarsénamina, interrumpidamente.

No debe perderse de vista que en los enfermos cardio-vasculares no se está tratando solamente la sífilis, ni la condición aórtica sífilítica; se está tratando muy especialmente un paciente con un corazón insuficiente o muy amenazado de insuficiencia para mantener una circulación adecuada. Esto quiere decir que el régimen y el tratamiento no han de circunscribirse a los métodos anti-sífilíticos sino que es preciso establecer un régimen y un tratamiento adecuados al estado funcional cardíaco y que la insuficiencia miocárdica (heart failure) ha de tratarse adecuadamente y aún primariamente a la condición sífilítica. A veces el avance del proceso patológico sífilítico es tal y las condiciones de insuficiencia circulatoria son tales, que es a esto último a lo que hay que dar atención casi exclusiva; el tratamiento anti-sífilítico ha de ocupar pues un puesto secundario. Dicho esto así, nos parece nuestro deber llamar la atención hacia la necesidad imperativa de conocer con toda la exactitud posible la condición cardiovascular de los candidatos al tratamiento anti-sífilítico sobre todo si la infección primaria data de 5 años o más, anteriores al

comienzo del tratamiento. El tratamiento de la sífilis meramente a base de las reacciones serológicas positivas en estos casos, en igual forma que en pacientes de reciente infección, puede traer consecuencias desastrosas; se habría conseguido en tales casos al tratar la sífilis, acelerar el quebranto de la salud o aún provocar la muerte del paciente, por la reacción desfavorable en el aparato cardio-vascular.

Los progresos sanitarios de nuestro país, el mayor conocimiento de las reglas de higiene, el desenvolvimiento natural demográfico de nuestro pueblo, lentamente van alterando nuestra composición poblacional. De un pueblo predominantemente joven, vamos convirtiéndonos en un pueblo de gente más vieja. El número de personas que han de presentar afecciones cardio-vasculares degenerativas ha de ir necesariamente en progreso como ha ocurrido en EE.UU. Al mismo tiempo que pueda ir reduciéndose las cifras de mortalidad por gastroenteritis, por tuberculosis, por malaria, por difteria, por tifoidea, por pulmonía, irán aumentando las muertes por diabetes, por cáncer, por nefritis, por arterioesclerosis, por enfermedades del corazón. Esto en cierto modo indicará un progreso sanitario en el país, pero demandará además una atención mayor a las enfermedades degenerativas y por ende a las enfermedades cardiovasculares. En estas la labor no es tanto de prevención (excepto en lo que a sífilis se refiere) como lo es de tratamiento, de alivio y de prolongación de la vida.

Los últimos 20 años han presenciado un desarrollo extraordinario en el estudio y mejor comprensión de las enfermedades cardio-vasculares. Los conceptos cuasi dogmáticos que privaban acerca de las mismas, han sido prácticamente abandonadas. Mientras hace 20 años la mayor preocupación parecía consistir en conocer el estado de las válvulas del corazón, su funcionamiento y su suficiencia, hoy el acento se pone en conocer el estado de salud del músculo cardíaco, su capacidad para mantener una circulación adecuada y su reserva de energías para afrontar las necesidades de la economía humana, adaptándose a las distintas actividades del individuo y a las condiciones valvulares que puedan existir. A los métodos de exploración clásica, de inspección, palpación, percusión y auscultación, se han agregado las investigaciones fluoroscópicas, radiológicas, y electrocardiográficas. Medidas tales como la de la capacidad vital, del tiempo de circulación, etc., son muy importantes. Un mejor conocimiento de las enfermedades del sistema hematopoyético, de los sistemas endocrinos, de las condiciones fisicoquímicas del organismo, del equilibrio de las sales del cuerpo, del efecto de la dieta, con especial relación a la influencia vitamínica, han aumentado ampliamente el radio de actividad del cardiólogo, porque al cabo no es el corazón un órgano aislado sino que es una de tantas ruedas cogidas dentro del engranaje fisiológico del cuerpo humano. Estos métodos nuevos de investigación más precisos han arrancado conocimientos a los secretos de las alteraciones del ritmo cardíaco, han permitido valorar mejor la significación de estas alteraciones, a veces sin importancia, otras de gran significación, y han permitido reconocer condiciones hasta hace poco más de 20 años prácticamente desconocidas, tales como los accidentes consecutivos a la estrechez o a la

oclusión de las arterias coronarias, muchas veces causa terminal de muerte en los enfermos del corazón.

La clasificación de los pacientes de enfermedades del corazón establecida por la Asociación de Enfermedades del Corazón de Nueva York está fundamentada en un criterio fisiológico.

Como se ve, esta clasificación está fundamentada más que nada en la capacidad del trabajo, sobre todo en las tres primeras clases. En cuanto a los criterios diagnósticos diremos, ampliando lo anteriormente dicho, que un examen cardiológico completo debe constar de los siguientes elementos:

1- Historial. Nada más importante para juzgar la condición cardíaca de una persona que la apreciación inteligente de la historia de su padecimiento que el propio paciente pueda ofrecer. Si ha tenido dolor en la región cardíaca o brazo izquierdo; si ha experimentado falta de aire, fatiga, cansancio y en que circunstancias; si tiene embarazo gástrico o dificultad respiratoria inmediatamente después de comer o después de un ejercicio que antes se efectuaba sin inconvenientes; si puede dormir descansadamente en posición horizontal o debe levantar la cabeza o el torso para respirar con mayor facilidad; si hay tendencia a hinchazón de los tobillos; si hay disminución de la orina; si la cantidad de orina es mayor por la noche que por del día y otro número de síntomas cuya duración, oportunidad y carácter, etc., iluminan grandemente la mente del médico para apreciar el desenvolvimiento del caso.

2-Examen físico. Es de suma importancia el examen físico, pero éste no puede concretarse exclusivamente al órgano cardíaco, ni siquiera al pecho. El examen del paciente tiene que hacerse necesariamente de cabeza a pies. El examen del fondo de los ojos puede revelarnos unas arterias tortuosas arterioescleróticas, la cual puede existir igualmente en el corazón, o puede revelarnos una degeneración luética de la retina que nos aclare la causa de otros fenómenos del corazón. Todo ello puede ser clave a la interpretación de los síntomas cardíacos. El examen de la garganta puede demostrarnos la presencia de infecciones focales, relacionadas con síntomas reumáticos. El examen abdominal nos hablará de las condiciones de los intestinos, hígado o estómago, que pueden hallarse en congestión pasiva por deficiencia de la circulación. El examen de las extremidades nos dirá de la presión venosa normal o alta, de los posibles edemas, de las deformidades de los dedos o de las uñas, etc., todos relacionados con males del corazón.

3-En tercer término ha de considerarse la exploración con los Rayos X. La imagen fluoroscópica del corazón nos dirá cual es su tamaño, cual es su contorno, cuales son las dimensiones de la aorta, cual es la relación de la viscera cardíaca respecto de los otros órganos que la rodean y si todo ello ha sufrido alteración. La radiografía permite las medidas exactas de los diámetros del corazón.

4-Luego los exámenes especiales: Los de laboratorio en general nos ayudan a determinar si nos estamos dando con un sífilítico, con un tuberculoso, o con un anémico. La metabolimetría nos dirá si nos damos con un hipertiroidismo o por lo contrario acaso con un mixedematoso incipiente. No hay que olvidar los aparatos para medir la

presión venosa; los de medir la presión arterial, los de medir la capacidad vital; las pruebas de ejercicio que puedan llevarse a cabo en distintas formas; el análisis químico de la sangre; el conteo de glóbulos y otros procedimientos de laboratorio y de clínicas, tales como la medida del tiempo de circulación ya mencionado, la sedimentación de eritrocitos, etc., etc., que no son del caso explicar ahora.

5-Por último llegamos al electrocardiógrafo, una de las adquisiciones más valiosas que ha hecho la cardiología en los últimos veinte años. Consta de un aparato que registra las variaciones eléctricas del corazón y a cuyo funcionamiento aludiremos brevemente.

Todo músculo al contraerse genera una corriente eléctrica. El corazón es un manojo de músculos; cada contracción suya es origen de una corriente eléctrica que se difunde por el cuerpo humano. Comunicado el cuerpo con el aparato registrador, si todos los demás músculos permanecen en reposo, la única corriente que puede registrarse es la generada por el corazón. En algunos casos es una prueba de corroboración, en otros prácticamente la única manera que tenemos de determinar si el corazón está indemne o ha podido padecer alguna injuria.

El trazado electrocardiográfico es sumamente interesante. Cada corazón tiene su trazado personal como cada persona tiene un carácter de letra. Se puede identificar una persona por su trazado cardíaco como se puede con su impresión digital. Pero los trazados en las personas sanas siguen, apesar de las variantes individuales, una norma común. Las alteraciones que rebasan estas

normas, responden a alteraciones patológicas del corazón.

En esta introducción al estudio de las enfermedades cardio-vasculares en Puerto Rico, me voy a permitir señalar lo que yo creo pudiera ser punto de arranque para interesantes estudios cardiológicos en esta isla. 1-La investigación de la incidencia y de la virulencia de las afecciones reumáticas incluyendo su distribución geográfica teniendo en cuenta la variedad climatológica que existe entre nuestra zona costera y nuestro interior montañoso. 2-Incidencia de la sífilis cardio-vascular en nuestro país y la eficacia de los métodos de tratamiento anti-sifilíticos para evitar las formas de sífilis cardio-vascular. 3-Investigación de la incidencia de la arterioesclerosis entre nosotros y de la enfermedad hipertensiva esencial o arteriolar. 4-Influencia de los factores vitamínicos en relación con nuestras costumbres dietéticas en las afecciones del corazón. 5-Incidencia y pronóstico de las formas degenerativas del corazón propiamente dichas (esclerosis y oclusiones coronarias principalmente). 6-Influencia general del clima, dados nuestras costumbres, y nuestra organización social. 7-Facilidades de tratamiento de las enfermedades cardio-vasculares en Puerto Rico.

NOTA EDITORIAL:

Debido a lo extenso del trabajo original el mismo ha sido editado en parte.

RVJ

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El Doctor Antonio Fernós-Isern: Nuestro Primer Cardiólogo

José M. Torres-Gómez, MD, FACP, FACC

El artículo (que yo desconocía) de nuestro *primer* cardiólogo, Dr. Antonio Fernós Isern, publicado hace 50 años cumplidos y escrito en un castellano impecable, analiza nuestros índices de mortalidad en aquel entonces, e incluye, además, unas predicciones que se han materializado a lo largo del tiempo. Es un artículo de primerísima importancia ya que parece representar el *primer* esfuerzo serio, no sólo en clasificar las primeras causas de muerte en nuestra Isla sino también en aclarar el por qué de su orden de magnitud y de las diferencias que existían con las de los EE.UU. Todo esto se expone haciendo énfasis sobre las enfermedades cardiovasculares.

Comienza el Dr. Fernós señalando que al unir las diarreas y enteritis (sin importar las edades de los enfermos) en una sola denominación (como debía ser) y al incluir las enfermedades renales en el renglón de las del corazón (como son en un número sustancial de ellas), las enfermedades cardiovasculares se convertían en la tercera (en vez de la séptima como aparecía entonces) causa de muerte en Puerto Rico.

La razón por la cual, aún haciendo estas modificaciones, no llegábamos a equipararnos con los EE.UU. (donde las enfermedades del corazón por sí solas ya eran la principal causa de muerte), se debía a nuestra alta incidencia de gastro-enteritis y tuberculosis (primera y segunda causas de nuestra mortalidad). Nuestra mortalidad infantil evitaba que, proporcionalmente, un número mayor de nuestra población llegaría a los 20 años, y otro número también sustancial de los que rebasaban esa edad, caían frente a nuestra tuberculosis, reduciéndose así nuestra población de mayor edad, cuando comienzan a aparecer las enfermedades degenerativas del corazón.

Me parece apropiado apuntar en este momento el hecho de que, aunque el programa de Unidades de Salud Pública (factor que ayudó a controlar nuestra tuberculosis) se estableció mayormente durante la incumbencia del Dr. Garrido Morales como Comisionado de Sanidad, el concepto, la planificación y el inicio de este programa emanó del Dr. Fernós, su antecesor, producto de un viaje oficial que hizo por el Sur de los EE.UU.

Alude el Dr. Fernós a la sífilis y a la enfermedad reumática como causas infecciosas de mortalidad. Aunque extremadamente rara en Puerto Rico, ya el Dr. Koppisch había encontrado patología reumática en algún que otro puertorriqueño y así lo hace constar el autor. En lo que sí hace incapié el Dr. Fernós, y con razón, es que desde el punto de vista de Salud Pública (y social), la sífilis cardiovascular sería el sector principal a atacar en un esfuerzo por disminuir la mortalidad por enfermedades del corazón en Puerto Rico. Era la enfermedad ante la cual se disponía "de armas efectivas y de conocimientos suficientes" para combatirla y evitarla. Llegó a causar el 26% de nuestras muertes repentinas (Koppisch). Era controlable, pero sólo si se trataban todos los afectados *adecuadamente*. Sólo así la enfermedad no se diseminaría. Y así llegó a suceder.

Esta medida era necesaria ya que existía una población que, librándose de la tuberculosis a los 40 años, moría de sífilis cardiovascular antes de los 65. Al desarrollar este tema, nuestro primer cardiólogo demuestra un conocimiento extenso y detallado no sólo de la enfermedad en sí, sino de las distintas modalidades del tratamiento y sus posibles complicaciones.

Que el Dr. Fernós está al tanto de los avances en la cardiología de su época se comprueba cuando habla sobre conceptos "prácticamente abandonados" y que "hoy el acento se pone en conocer el estado de salud del músculo cardíaco" y no tanto "en el estado de las válvulas del corazón". ¡Esto es aplicable a la cardiología de hoy!

Cita en nuestra literatura médica, creo por primera vez, la clasificación de los enfermos del corazón establecida por la Asociación de Enfermedades del Corazón de Nueva York (criterio fisiológico).

Termina su artículo el Dr. Fernós señalando la importancia que tienen el tomar un historial *completo* y detallado del padecimiento del enfermo, y el hacer un examen físico de *todo* el paciente y no "concretarse exclusivamente al órgano cardíaco, ni siquiera al pecho". Comenta sobre la ayuda que se puede obtener del laboratorio, Rayos X y, últimamente, de la electrocardiografía en el diagnóstico de enfermedades del corazón. Aquí ofrece siete "puntos de arranque para interesantes estudios cardiológicos en esta isla". Su visión fue tan clara que ya, 50 años más tarde, sus recomendaciones se han realizado, lográndose así un conocimiento de la situación cardiovascular que hoy existe en Puerto Rico y de las medidas que hay que seguir tomando para la prevención de su incidencia y la reducción de su mortalidad. Obviamente, al tiempo que se escribe ese artículo, todavía no han aparecido en el horizonte médico las amenazantes figuras de la hipertensión, la endocarditis bacteriana, y las cardiomiopatías que más tarde van a afectar seriamente los índices de mortalidad.

Como bien lo predice el Dr. Fernós, "los progresos sanitarios de nuestro país", "el desenvolvimiento natural demográfico de nuestro pueblo" (desplazamiento del campo hacia la ciudad), y "el mayor conocimiento de las reglas de higiene" alterarán nuestra composición poblacional. Al reducirse las cifras de mortalidad por gastroenteritis y tuberculosis, malaria, difteria, tifoidea y otras enfermedades infecciosas, se irá prolongando nuestra longevidad y comenzaremos a morir por diabetes, cáncer, arterioesclerosis y enfermedades del corazón. Y entonces nos acercaremos a las estadísticas de los EE.UU. y así ha sucedido.

Más se podría deducir de este histórico artículo pero me detengo aquí porque, de lo contrario, me expondría a que el lector creyera que estoy exagerando. Nada de eso. Lo que de hecho sucede es que el Dr. Antonio Fernós Isern, nuestro *primer* cardiólogo, lo fue en todo el sentido de la palabra.

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MEDICAL ASPECTS OF NUTRITION

Metabolic Control of Food Intake*

Mark I. Friedman, Ph.D.**

The intense concern with body weight control in the United States is matched, if not surpassed, by a passionate interest in food and in finding ways to make it appealing. It is therefore no surprise that overeating and obesity are often believed to be caused by the availability and variety of palatable foods. What is surprising, however, is that this belief, which is so widely held among nutrition professionals, has virtually no scientific evidence to support it. On the contrary, a growing number of studies indicates that changing the palatability of food, without altering food composition, has no effect on caloric intake or body weight gain.¹ This is not to say that the sensory properties of food are unimportant in determining food preferences; clearly, we choose food that is appealing to our senses. Nor does it deny that the sensory properties of food can affect food intake in the short term.² Rather, the results indicate that over a longer, nutritionally significant interval, food intake is determined by factors other than the palatability of the diet. Elucidating these mechanisms of food intake control should contribute greatly to our understanding of the causes of overeating during the development of obesity.

For many years, food intake has been thought to be governed by signals generated in the postabsorptive utilization and storage of metabolic fuels. This article will provide an update on current thinking about the nature of these metabolic signals, where they are detected, how they are linked to body fat reserves and their role in hyperphagia and obesity.

The Metabolic Signal

Although there is substantial evidence that changes in energy metabolism influence food intake, the specific metabolic signals have not been identified. In general, the search for signals has concentrated on glucose and fat

metabolism. Recent studies showing that decreases in glucose and fatty acid utilization produce synergistic increases in food intake. This provides strong evidence that information derived from the metabolism of glucose and fat fuels is integrated in some fashion to control food intake.³ However, it is not clear how this integration is accomplished.

According to the traditional view, two separate metabolic stimuli control food intake.⁴ A "glucostatic" signal, generated by changes in intracellular glucose utilization, is thought to operate in the short-term to control meal-to-meal feeding behavior, while a "lipostatic" signal associated with body-fat reserves governs food intake over a longer period. The two signals are seen working in a coordinated fashion in which the lipostatic control modulates the impact of short-term glucostatic signals. This integration is believed to occur at a neural level via interactions among separate brain systems mediating the two controls.

Another model for the metabolic control of food intake is based on the notion that an event common to the intracellular metabolism of glucose and fat provides the signal controlling food intake. In this case, changes in glucose and fat metabolism that influence food intake are integrated at a molecular level. It has been suggested that intramitochondrial oxidation, a final common path for the utilization of all metabolic fuels, generates a stimulus for the metabolic control of food intake.⁵ Relative increases in fuel oxidation result in decreases in food intake, whereas reductions in fuel oxidation increases it. Here, oxidation refers to fuel oxidation in a nonmuscular tissue that is coupled to the production of a useful form of biochemical energy such as adenosine triphosphate (ATP). This model is particularly promising both for its parsimony and its capacity to account for a wide range of observations related to feeding behavior and food intake control.

The Site of Detection

In order to affect food intake, changes in metabolism must be detected by the nervous system and translated

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into changes in eating behavior. Typically, sensors for the metabolic signals controlling feeding are thought to be located in the brain, but the evidence is not compelling.⁵ Although damage to various brain areas disrupts the eating response to experimentally induced changes in metabolism, brain lesions that interfere with the changes in food intake after metabolic treatments produce nonspecific, motivational deficits which alone can hamper the feeding response.⁶ Whereas administration of metabolic substrates or inhibitors into the brain or cerebral ventricles alters food intake, direct manipulation of brain metabolism also alters peripheral metabolism. Thus, it is not clear whether cerebral administration of metabolic substrates or inhibitors affects food intake directly by activating sensors in the brain or indirectly by stimulating peripheral metabolic receptors for feeding.

A peripheral sensor for the metabolic control of food intake was first suggested by Russek. He proposed that the liver contained receptors which are sensitive to changes in hepatic metabolism.⁷ His initial experiments showing that food intake could be inhibited by infusions of glucose into the hepatic portal vein, but not jugular vein, provided strong evidence to support a hepatic control of feeding. Recent studies have confirmed this finding and have also demonstrated that the differential effect on food intake of portal versus jugular vein infusions of sugars is related to their different metabolic effects on the liver.^{8, 9} Additional support for a hepatic control of food intake stems from studies showing that food intake is decreased by intravenous infusions of fructose, which is utilized primarily in the liver, and that cutting the hepatic branch of the vagus nerve reverses this effect of fructose.^{9, 10}

Changes in hepatic metabolism may not only control food intake, but may also shape food preferences. Laboratory rats develop a preference for a food flavor consumed at the same time glucose is infused in the portal vein.⁸ This rewarding effect does not seem to be specific to glucose, however, as oral ingestion of either glucose or fat will also create a learned flavor preference.¹¹ Moreover, the formation of a conditioned preference apparently depends on the ability to oxidize the ingested fuel.¹¹ Thus, it appears that the metabolic signal which determines how much food is consumed may be the same as that which, through association with flavor cues, can determine what is consumed. The preference for a food based on its sensory properties may depend, therefore, on the metabolic effect of that food.

Overeating and Obesity

The role of body fat reserves in the control of food intake has been suspected for many years.¹² Much of the research effort to link body fat with feeding stems from the hypothesis that a blood-borne signal correlated with the degree of adiposity controls food intake; however, despite extensive efforts, there is no clear evidence that such a signal exists.¹² Another, less explored, view is based on an indirect relationship between fat reserves and food intake in which lipid deposition affects feeding by buffering the metabolic signals that control food intake.¹³ This hypothesis is accommodated easily by a theory of food

intake based on a signal from fuel oxidation. In this case, the role of body fat reserves in the control of food intake is seen in terms of the partitioning of fuels between storage and oxidation.¹³ Displacements from a normal or steady-state equilibrium between fuel storage and oxidation affect food intake by altering the signal generated by the oxidation of fuels.

According to this perspective, factors which increase the deposition of fuels in fat stores and thereby produce a relative decrease in the oxidation of fuels as described above would be expected to increase food intake. On the other hand, use of fuels for storage instead of for incomplete oxidation to produce heat (thermogenesis) or for muscular activity should not affect food intake even though it may increase body fat. A number of animal studies have demonstrated that increased fat storage is independent of the overeating that is characteristic of the weight-gain phase in a variety of obese animal models.^{5, 13} This indicates that excessive lipid deposition may be a cause, not only a result, of overeating. In this light, hyperphagia during the development of obesity is an attempt to compensate for a "loss of otherwise oxidizable fuels into storage. The decrease in energy expenditures observed in pre-obese¹⁴ or previously obese¹⁵ humans may reflect this shift in fuel partitioning away from oxidative pathways.

Dietary Hyperphagia

Shunting of fat fuels into storage and away from oxidative pathways may underlie the hyperphagia associated with feeding high-fat diets to laboratory animals. Typically, these diets are not only high in fat, but also contain large amounts of carbohydrate, which would stimulate insulin secretion. Because insulin promotes the storage of fat and inhibits its oxidation, it is possible that the carbohydrate portion of these high-fat diets is as important as the fat in promoting overeating. This is supported by the observation that insulin treatment counteracts the satiating effect of fat in laboratory rats.¹⁶ High-fat diets that induce overeating also may provide a large stimulus for insulin secretion because they tend to be high in caloric density and usually contain little fiber, which together would accelerate gastric emptying of carbohydrate.¹⁷ There is no overeating when a high-fat diet is formulated to avoid an increase in energy density.¹⁸

The typical American diet is also high in both fat and carbohydrate with about 40% of calories supplied from each. Whether this combination contributes to overeating and obesity in humans is unknown. However, several observations raise the possibility that dietary fat calories may bypass the metabolic control of food intake because they are "lost" into adipose tissue. Ingestion of fat does not appreciably increase energy expenditures in human subjects eating a mixed (carbohydrate and fat) diet.¹⁹ In addition, humans do not adjust caloric intake appropriately when the fat content of their mixed diet is varied.²⁰ Human volunteers also do not adjust oral caloric intake accurately during intravenous feeding of lipid.²¹ This suggests that the lack of compensation to changes in fat ingestion may be due to a failure to engage a post-absorptive metabolic control of food intake.

Summary

A specific biochemical mechanism for the metabolic control of food intake has not been identified. However, a theory based on a signal generated from the oxidation of metabolic fuels and detected in the liver offers a powerful, integrative framework that helps explain a number of phenomena related to feeding behavior. In addition to providing a metabolic basis for the formation of conditioned food flavor preferences, a control of food intake by fuel oxidation provides a mechanism for overeating in the dynamic phase of obesity and hyperphagia produced by high-fat diets.

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VIII SCIENTIFIC MEETING INTER-AMERICAN SOCIETY OF HYPERTENSION

**ORGANIZED BY:**

The Organizing Committee of the
8th Inter-American Society of Hypertension

UNDER THE AUSPICES OF:

The Inter-American Society of Hypertension

SPONSORED BY:

Puerto Rico Society of Nephrology and Hypertension

IN COOPERATION WITH:

University of Puerto Rico School of Medicine

GENERAL INFORMATION

DATE: May 13 - 17, 1989

SITE: Caribe Hilton International Hotel,
San Juan, Puerto Rico

SATELLITE SYMPOSIA

Satellite symposia are also planned.

May 13 (Sat.) - 17 (Wed.), 1989
SAN JUAN, PUERTO RICO

IMPORTANT DATES


Deadline for receipt of abstracts November 21, 1988

Notification of Abstract acceptance January 30, 1989

Deadline for pre-registration March 15, 1989

The Planning Committee of the 8th
Inter-American Society of Hypertension
c/o Sociedad de Nefrología de P.R., Inc.

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SOCIOS NUEVOS



ACTIVOS

Burgos Valentín, Bolívar MD - Escuela de Medicina de la Universidad de Zaragoza, España, 1976. Pediatría. Ejerce en Humacao.

Cantillo Govantes, Joaquín MD - Escuela de Medicina de la Universidad de Puerto Rico, 1984. Anestesiología. Ejerce en San Juan.

Casillas Santos, Emilio MD - Escuela de Medicina de la Universidad de Granada, España, 1969. Otorrinolaringología. Ejerce en Bayamón.

Mercado Arroyo, Alejandro MD - Escuela de Medicina de la Universidad Nacional Pedro H. Ureña, República Dominicana, 1977. Neumología. Pediatría. Ejerce en Bayamón.

Ortiz Domenech, Ramón E. MD - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, 1973. Medicina General. Ejerce en Río Piedras.

Palmer López, Arnaldo MD - Hahnemann Medical College, Philadelphia, Pennsylvania, 1941. Cirugía. Ejerce en Santurce.

Príncipe López, Jorge Luis MD - Escuela de Medicina de la Universidad de Santiago de Compostela, España, 1976. Medicina Interna. Ejerce en Bayamón.

Rodríguez Pombar, Miriam A. MD - Escuela de Medicina de la Universidad de Valladolid, España, 1980. Medicina General. Ejerce en Patillas.

INTERNOS-RESIDENTES

Devarie Díaz, Norma A. MD - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1984. Medicina Interna.

Romero Basso, Juan Luis MD - Louisville University Medical School, Louisville, Kentucky, 1983. Ortopedia.

YOCON[®]

YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the CNS and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

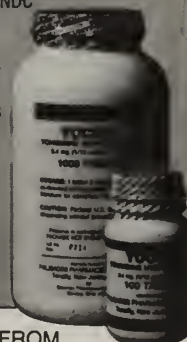
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
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ASOCIACION MEDICA DE PUERTO RICO

BOLETIN

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquina a doble espacio, por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej. MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábiga) y el autor. Debe indicarse la parte superior de la ilustración.

Resumen

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

1. Para artículos de revistas: Apellido(s) e iniciales del nombre del autor(es), título del artículo, nombre de la revista, año, volumen, páginas. Por ejemplo:
Villavicencio R. Soplos inocentes en pediatría, *Bol Asoc Méd P Rico* 1981; 73: 479-87.
Si hay más de 7 autores, incluir los primeros 3 y añadir et al.
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Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquina a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

*Estas "Instrucciones para los Autores" son de acuerdo a las normas establecidas por el Comité Internacional de Editores de Revistas Médicas en sus "Requisitos Uniformes para Manuscritos Sometidos a Revistas Bio-Médicas".

INSTRUCTIONS TO AUTHORS*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

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1. For periodicals: Surname and initials of author(s), title of article, name of journal, year, volume, pages. For example:
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If there are more than 7 authors list only 3 and add et al.
2. For books when the authors of the cited chapter is at the same time the editor: Surname and initials of author(s), title, edition, city, publishing house, year and page. For example:
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Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

*The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

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EL NUEVO
CARDIZEM[®] SR
(diltiazem HCl) cápsulas de liberación
sostenida

Para la hipertensión

Sírvase ver el breve resumen de información para prescribir en la última página.

90 mg SR bid

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Demuestra una eficacia semejante a la de los bloqueadores beta y diuréticos en una gran variedad de pacientes.²⁻⁵

Raramente relacionado con fatiga, somnolencia, depresión, estreñimiento, disfunción sexual o hipotensión postural.^{2-5,7-8 *}

Conserva o mejora la capacidad para el ejercicio.⁸

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Mejora la circulación sanguínea a órganos señalados, incluyendo el riñón y el corazón.⁹

Conserva la función renal sin perturbar el equilibrio líquido o electrolito.¹⁰

Reduce la hipertrofia⁶ ventricular izquierda y no afecta a los lípidos séricos desfavorablemente.^{2,5,11}

*Por favor, lea en la proxima página, la seccion de efectos secundarios en el resumen informativo para recetar.

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CARDIZEM[®] SR

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Para la hipertensión



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90 mg bid*

**Disponible también:
Cápsulas de 120 mg**

*La dosis debe ajustarse a la necesidad de cada paciente, empezando con 60 a 120 mg, dos veces al día.

BRIEF SUMMARY

CARDIZEM[®] SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

- Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment,

may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use of CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and dunning marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS		
Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than have been observed in angina trials. In many cases, the relation to uncertain).

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, atrial extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, numbness, paresthesia, personality change, tremor, abnormal dream.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT and LDH (see hepatic warnings), vomiting, weight loss, thirst.

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye inflammation, hyperglycemia, sexual difficulties, nasal congestion, osteoarthral pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme and leukopenia. Definitive cause and effect relationship between these and CARDIZEM therapy cannot yet be established.

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SMOKING IS BECOMING INCREASINGLY A HABIT OF THE LESS EDUCATED: REPORTS

Smoking in the United States is becoming increasingly a health risk of the less educated and the socioeconomically disadvantaged, say studies in the *Journal of the American Medical Association*.

National trends in smoking prevalence from 1974 through 1985 show that education has replaced gender as the major sociodemographic predictor of smoking status, say the authors, John P. Pierce, PhD, Michael C. Fiore, MD, and colleagues at the Centers of Disease Control (CDC), Atlanta. Their three studies of smoking trends are part of a *JAMA* theme issue on health issues related to smoking. Two related studies in this issue examine smoking prevalence among pregnant women and among U.S. Hispanics, and conclude that much needs to be done to help smokers in these groups quit.

"Smoking prevalence has declined across all educational groups but the decline has occurred five times faster among the higher educated compared with the less educated," Pierce and colleagues write. From 1974 to 1985, smoking prevalence among persons with less than a high school diploma declined from 36.3 percent to 34.2 percent, but prevalence among those with four years or more of college fell sharply, from 28.5 to 18.4 percent. However, the prevalence of smoking among young women with less than a college education actually increased to an all-time high of 44.4 percent in 1985, they report.

Their studies, based on data collected by the National Center for Health Statistics through the National Health Interview Surveys, project rates for cigarette smoking prevalence, initiation and cessation through the year 2000. If current trends continue, the authors predict that 22 percent of the population aged 20 and older in the year 2000 will smoke, compared to 30 percent in 1985. While less than 10 percent of college graduates will be smokers, at least 30 percent of those with no more than a high school education will smoke. The large and widening educational gap in smoking suggests that anti-smoking messages must be based much more on educational status, they conclude.

The authors also found that smoking prevalence is decreasing across all race-sex groups, although at a slower rate for women than men, and that differences in initiation more than cessation are primarily responsible for the converging of smoking prevalence rates among men and women. "From 1974 to 1985, the prevalence of smoking among men decreased at a consistent rate of slightly less than one percentage point per year," they report. "During the same period, the prevalence of smoking among women also fell, but at a rate only one third of that observed for men." If these trends continue, smoking prevalence among males will drop to about 29 percent in 1990 and 20 percent by 2000, while prevalence among women will decrease to 26 percent by 1990 and 23 percent by 2000—which means that after 1995 the number of women who smoke may exceed the number of male smokers.

Although the health profession's war against "the number one preventable cause of death in the United States" has helped approximately 1.3 million smokers to quit each year between 1974 to 1985, every year during the early 1980s about 1 million young persons joined the ranks of regular smokers, the authors report.

The authors estimate that the percentage of blacks who smoke will fall to about 32 percent by 1990 and to 25 percent by the year 2000, while the percentage of white smokers should fall to about 27 percent in 1990 and 21 percent by the year 2000.

In another *JAMA* study, data from the 1982-1983 Hispanic Health and Nutrition Examination Survey was used to estimate the smoking prevalence of U.S. Hispanics. Although smoking prevalence has decreased among Hispanic men, it has increased among Cuban-American and Puerto Rican-American women, report the authors, Luis G. Escobedo, MD, SM, MPH, and Patrick L. Remington, MD, MPH, of the CDC. They conclude that better intervention efforts must be targeted toward these groups.

Another study in *JAMA* examined the prevalence of smoking among pregnant and nonpregnant women. The authors, David F. Williamson, PhD, and colleagues at the CDC, examined data collected in 1985 and 1986 from 26 states in the Behavioral Risk Factor Surveillance System, to see if it is likely to meet the U.S. Public Health Service's goal of reducing the smoking rate in pregnant women to less than half the overall rate in women by 1990. The authors found that pregnant women were only 30 percent less likely to be current smokers than were nonpregnant women. Even worse, unmarried pregnant white women were 40 percent *more likely* to smoke than their nonpregnant counterparts. "We conclude from this analysis that the 1990 health objective for smoking among pregnant women is unlikely to be achieved," they write. "Clinicians providing care to pregnant women need to pay increased attention to smoking cessation."

In an accompanying editorial, U.S. Surgeon General C. Everett Koop, MD, SCD, comments on the tremendous gains in reducing the prevalence of smoking in the quarter century that has passed since the first Surgeon General's report on the health hazards of smoking. Physicians and other health care providers can rejoice over these gains, he says, "but only for a moment." Koop warns against complacency since 50 million Americans still smoke and more than 300,000 continue to die each year of smoking-attributable disease.

Although cigarette sales are declining, "the cigarette industry remains one of the most profitable and powerful businesses in America," Koop writes. "It uses its vast economic strength to defend the promotion, sale, and use of tobacco and to punish those who stand in its way." However, if fully tapped, the collective influence and moral strength of the medical profession "can overcome the tobacco industry's attempt to maintain the nation's addiction to nicotine."

The Surgeon General calls on physicians to continue encouraging and helping smoking patients to quit, and to urge elected officials to support tobacco-control policies, including a ban on advertising and measures to halt the exportation of tobacco-caused disease, disability, and death to people in developing countries, who are increasingly becoming major targets of aggressive marketing by U.S. and British tobacco companies.

JAMA January 6, 1989

STUDIES: TOBACCO AD WARNINGS LOST ON TEENS, UNREADABLE IN MOST OUTDOOR ADS

The federally mandated warnings on tobacco advertisements don't seem to be very effective public health messages when it comes to adolescents, and are unreadable in their current form in most outdoor ads, two studies in the *Journal of the American Medical Association* conclude.

A third report in the same *JAMA*, a special theme issue on smoking, indicates that an aggressive community-based campaign can sharply reduce illegal over-the-counter store sales of cigarettes to minors. However, such an effort does not appear to affect similar sales from vending machines.

The Surgeon General's warnings on tobacco ads were first ordered in 1972 in an effort to educate the public about the health dangers associated with tobacco. But there have been few published studies on the effectiveness of these warnings as a health message, notes the first *JAMA* report, by Paul M. Fischer, MD, of the Medical College of Georgia, Augusta, and colleagues. To test this in adolescents, the authors used well-accepted market research methods to examine whether 61 study subjects aged 13 to 17 read and recalled the Surgeon General's warnings when viewing five different tobacco ads in magazines.

Using a technique called eye tracking —monitoring how the subjects' eyes moved across and ad—the authors found that average viewing time of the Surgeon General's warning amounted to only 8 percent of the total advertising viewing time. In nearly 44 percent of cases, the warning was not viewed at all.

Following the ad viewing, study subjects were asked to identify the observed warnings from a list that included other simulated warnings. They did "only slightly better than random guessing" in this test, the authors report.

"Using market research criteria, the federally mandated warning must be viewed as an ineffective public health message in so far as adolescents are concerned," they conclude. "Our data indicate that adolescents often do not see the warning in tobacco advertisements. Even when seen, there is little, if any, reading of the warning... If the warnings are not seen, or seen but not processed, they are extremely unlikely to be effective in countering the promises of power, romance, and fun implied by tobacco advertisements."

In a related study, Ronald M. Davis, MD, and Juliette S. Kendrick, MD, of the Centers for Disease Control, Rockville, Md., investigated the readability of the Surgeon General's warning in cigarette ads on outdoor billboards and taxicabs. In an experiment done in the Atlanta area under typical driving conditions, observers were able to read the entire health warning on 18 of 39 street billboards but only two of 39 highway billboards, the authors say. "In contrast, the content of the ads (ie, name, other wording and notable imagery) could be recognized under the same conditions on more than 95 percent of the billboards."

In a similar study of 100 taxicab cigarette ads in New York City, observers could not read the health warning in any of the ads but were able to identify the name in all ads and notable imagery in 95 percent, the study reports.

"We conclude that the Surgeon General's warning is not readable in its current form in the vast majority of billboard and taxicab ads," the report says. "Factors contributing to unreadability include the small size of the letters, the excessive length of the warnings, the distance between the viewers and the ads, and movement between the viewers and the ads."

In the third *JAMA* study, David G. Altman, PhD, of the Stanford University School of Medicine, Palo Alto, Calif., and colleagues describe an effort to stop illegal cigarette sales to minors in Santa Clara County, Calif. The project involved an aggressive six-month campaign using communitywide media, direct merchant education, contact with the chief executive officers of chain stores and franchise operations owned by major companies, and grassroots work with community groups.

The researchers recruited 18 minors aged 14 through 16 who, in January 1988, visited 412 stores that sold cigarettes over the counter and 30 outlets that had cigarette vending machines. The youths were able to buy cigarettes at 74 percent of the stores and from all of the vending machines, the report says.

Following the six-month campaign to educate the community, merchants and chain store executives about the problem of illegal tobacco sales to minors, the youths

again tried to buy cigarettes at the stores and vending machines. Illegal store purchases were reduced to 39 percent, although machine sales were unaffected.

"These encouraging finds must be balanced by what remains to be accomplished," the authors conclude. "If we are ever to achieve a tobacco-free generation we must eliminate the sale of tobacco to minors. While much remains to be accomplished in achieving this goal, the findings of this study illustrate that an aggressive community and merchant education program can be effective."

In an accompanying editorial, Donald E. Greydanus, MD, of Des Moines, says the project described by Altman and his colleagues had limitations and will not be easy to reproduce on a larger scale. But even if it is "not the final word in solving the problem of illegal tobacco sales to youngsters, it clearly is a welcome step," he writes.

"The numerous negative health effects of tobacco are well-known, yet our youths continue to be seduced into tobacco addiction, and our society, incredibly, tolerates this massive, potentially suicidal behavior," Greydanus says. "It is amazing that we sit back and allow this modern-day Pied Piper of Hamelin to lure our children away from their good health and to their eventual self-destruction. Health care professionals must recognize this danger and help rescue our children."

"The authors' efforts extending the work of others in this field could move us a bit closer to our goal of a tobacco-free youth: Their research is grounded in important literature that documents that if we can delay the onset of tobacco (and other drug) experimentation from early to late adolescence, the result will be fewer adults addicted to tobacco. Reducing easy access to tobacco along with educating youth (and society) about its many dangers is a good beginning!"

JAMA January 6, 1989

NICOTINE PASSED TO BREAST-FEEDING BABIES

Smokers who breast-feed appear more likely to have infants with colic than non-smoking breast-feeding mothers, a letter in the *Journal of the American Medical Association* says. Authors Ingrid Matheson, MScPharm, and Gro Nylander Rivrud, MD, of the University of Oslo, Norway, studied 885 mothers in Norway and found 40 percent of the babies breast-fed by smokers showed signs of colic—crying more than two to three hours a day at least four days a week, compared with 26 percent of the infants of non-smokers. In addition, more smokers than nonsmokers reported stopping breast-feeding early because of "too little milk," the authors say. They say nicotine is found in breast milk in notable concentrations and suggest "other substances in tobacco probably are excreted in breast milk." Breast-feeding mothers "should be advised not to smoke" or at least to reduce the number of cigarettes "to a minimum," they say.

JAMA January 6, 1989

PASSIVE FREEBASE COCAINE INHALATION BY CHILDREN

Various reports have described the addictive effects that maternal cocaine abuse can have on a fetus or newborn. But a report in January's *American Journal of Diseases of Children*, *AJDC*, describes a different problem—apparent passive inhalation of freebase "crack" cocaine vapors by infants and toddlers. Authors David A. Bateman, MD, and Margaret C. Heagarty, MD, of Harlem Hospital, New York City, describe four such cases in which cocaine and its principal metabolite were isolated from the urine of four hospitalized children aged 3 to 47 months, all of whom had been exposed to smoke from freebase cocaine used by their parents or adult caretakers. Two children had transient neurological symptoms and two had seizures of indeterminate cause. "Passive cocaine inhalation may have caused or contributed to these symptoms," the authors say. "Children in the care of adults who abuse freebase cocaine should be considered at risk not only for disruption of their social environment but also for the effects of cocaine toxicity."

NASAL SYMPTOMS ASSOCIATED WITH ADOLESCENT COCAINE ABUSE

Physicians should consider cocaine abuse as a cause of puzzling or stubborn rhinitis (runny nose) even in teenagers, says a report in January's *Archives of Otolaryngology-Head and Neck Surgery*. The study, by Richard H. Schwartz, MD, of the Fairfax Hospital, Falls Church, Va., and colleagues, bases the conclusion on a survey of 464 adolescents on cocaine use patterns and associated nasal effects. Respondents were enrolled in seven outpatient substance abuse treatment facilities around the country. Nearly three-fourths of those surveyed said they abused cocaine at least once before entering treatment. Cocaine use was linked to various nasal symptoms, the number of which increased with greater drug use. Frequent sniffing was the most common symptom, with a diminished sense of smell or self-diagnosed "sinus" problems also prevalent complaints. The authors suggest that "in addition to consideration of symptoms that may be caused by misuse of topical vasoconstrictor nose spray, the astute otolaryngologist should consider cocaine abuse as a cause of recalcitrant nasal symptoms."

PARENTAL AGE RELATED TO ALZHEIMER'S DISEASE?

People born to parents of advanced age may be at higher risk of developing Alzheimer's disease later in life, a study in January's *Archives of Neurology* suggests. The

study, by Katsuya Urakami, MD, and colleagues at the Tottori University School of Medicine, Yonago, Japan, involved 77 Alzheimer's patients; 52 patients with a different type of dementia, multi-infarct dementia, or MID, which is caused by small strokes; and 91 controls. The authors then looked at how old the study subjects' parents were when the subjects were born. Those mean maternal and paternal ages were significantly higher in the case of the Alzheimer's patients than for the MID patients or the controls, the researchers say. "This study suggests that advanced age may become a cause of chromosomal abnormality, and advanced parental age at subjects' birth may be a possible risk factor in developing (Alzheimer's disease)," the authors conclude.

SOLUTION DRAMATICALLY EXTENDS LIVER GRAFT PRESERVATION TIME

A solution developed by University of Wisconsin researchers can greatly extend preservation time for livers scheduled for transplantation, maintaining graft viability for up to 24 hours without apparent damage, a study in the *Journal of the American Medical Association* reports.

The inability to preserve donor livers beyond the few hours provided by initially cooling the organ has been a key obstacle in transplant surgery. But by dramatically increasing this safety margin, the University of Wisconsin (UW) solution has the potential for a "revolutionary effect" on liver transplantation, concludes the study by Satoru Todo, MD, and colleagues at the University of Pittsburgh and the Veterans Administration Medical Center, Pittsburgh.

The new study compared the outcomes of 185 cadaver liver grafts (164 patients) preserved for four to 24 hours with UW solution, and 180 grafts (152 patients) preserved for three to 9 1/2 hours with conventional "Euro-Collins solution." "Although the average preservation time of the UW-preserved livers was almost twice as long as that of the Euro-Collins-preserved livers," the authors say, "the UW-preserved grafts survived at a higher rate; permitted equal patient survival; and had a lower rate of primary non-function, a reduced need for retransplantation, and a lower rate of hepatic artery thrombosis."

Patient survival times after three months were 83 percent with the UW-preserved livers compared with 81 percent with the conventionally preserved grafts, and 81 and 77 percent, respectively, after six months. Graft survival, however, was better in the UW livers—76 percent at three months and 73 percent at six months for the UW livers vs. and 65 percent for the Euro-Collins group.

The researchers also report no correlation between the preservation time of the UW-preserved grafts and liver function abnormalities in the first week following transplant surgery. In contrast, livers preserved with the Euro-Collins solution for more than five hours had significantly increased liver function test abnormalities, the authors say.

Euro-Collins solution was first used in 1967 in liver transplantation and has been the standard preservative

for potential donor livers since then. Use of the UW preservative solution first was described in liver transplantation in 1987. Euro-Collins solution contains only electrolytes and glucose, while the UW solution has other additives—including hormones, amino acids and sugars—designed to help preserve the organ and maintain its integrity.

"The remarkable effectiveness of the UW solution has revolutionized liver transplantation at almost every level," the Pittsburgh researchers conclude. "The enhanced margin of safety has permitted more effective use of organs that can be stored safely while waiting for operating room facilities or personnel to become available. It has allowed procurement of grafts from cities once considered too distant, from as far as across the Atlantic Ocean."

The added preservation time also allows closer scrutiny and testing of the donor graft for transplant suitability before taking a potential recipient to the operating room, the study says. And it allows surgeons more time to operate.

Ironically, the authors note, while the advantages of the UW solution are so obvious, the reasons that it works remain unclear, although a key point may be its apparent ability to reduce cell swelling in the organ destined for transplantation.

JAMA February 3, 1989

GUIDELINES FOR TRAVELING AND VACATIONING WHILE PREGNANT

If precautions are taken and general health guidelines followed, pregnant women can travel for business or pleasure without harming themselves or their fetuses, says a report in the *Journal of the American Medical Association*.

"The special problems of travel during pregnancy have become clinically important as more women are traveling to remote places for business or recreation," say Michele Barry, MD, and Frank Bia, MD, MPH, of Yale University School of Medicine, New Haven, Conn. But with few exceptions, pregnant women can travel safely, provided they take certain precautions and make some preparations.

Domestic airlines restrict air travel for women beyond the 36th week of gestation and most foreign airlines will not take pregnant passengers after their 35th week, the authors report. Some airlines may require a physician's note specifying expected date of birth. Many health insurance carriers do not cover delivery in a foreign country or even hospitalization for premature labor. Pregnant patients should check whether such restrictions apply before traveling, they recommend.

Air pressure in commercial jetliners flying at high altitudes is maintained at the pressure of air 5,000 to 8,000 feet above sea level, they report. While this reduced air pressure usually causes no problems for normal pregnant women and their fetuses, it may be harmful for seriously anemic patients and those with sickle cell

anemia, and may require the use of supplemental oxygen while in flight. To prevent additional blood-oxygen deficits from exposure to carbon monoxide, pregnant women should request a seat in the plane's non-smoking section, the authors suggest.

To reduce the chance of developing blood clots, which occur more frequently during pregnancy, pregnant women should avoid sitting for extended periods of time. By requesting an aisle seat, they can get up more easily to walk about the cabin. While seated, seat belts should be worn low around the pelvis.

Pregnant women should be discouraged from vacationing at altitudes above 7,000 feet, the authors say. "The remoteness of trekking areas, the high incidence of enteric infections, and the lack of suitable medical care should be emphasized to those contemplating such treks," they write.

The authors say strenuous exercise, such as running or jogging, need not be curtailed during pregnancy, provided it is not physiologically threatening to mother or fetus and doesn't cause overheating. Although swimming is an excellent exercise for the pregnant vacationer, they advise against waterskiing and scuba diving to depths below 60 feet.

Because of the danger of infection with malaria that is resistant to the relatively safe anti-malaria drug chloroquine, pregnant women should give serious thought before traveling to east Africa, Thailand, and other areas where chloroquine-resistant malaria is endemic, the authors report. They also offer guidelines for immunizations against diseases that may be encountered while traveling. When immunizations are clearly needed, the risk to mother and fetus from the disease itself must be balanced against the risk to both from immunization, they write. Whenever possible, immunizations should be avoided, especially during the first trimester.

"As a general rule, most live vaccines are best avoided entirely; however, there are circumstances during which even they can, and should be, administered during pregnancy," they write. Greater emphasis should be placed on other means of prevention—such as using water purification technique to prevent typhoid—rather than on immunization. "Common sense dictates that travel should be avoided if multiple births are expected or if there is a history of pregnancy-induced hypertension or bleeding," the authors say. They say pregnant women should also remember that "vehicular injuries are the major cause of death in travelers, and seat belts should not be avoided by the pregnant traveler simply because of discomfort." If these guidelines are followed, pregnant women can travel with confidence, they conclude.

JAMA February 3, 1989

AIDS INCIDENCE, LATENCY SAME FOR HOMOSEXUAL, HEMOPHILIC MEN: STUDY

The incidence and latency period for AIDS appears to be the same for homosexual and hemophilic men infected with the human immunodeficiency virus (HIV), says a

study in the *Journal of the American Medical Association*.

It is not known whether risk groups, such as intravenous drug abusers, homosexuals, and patients exposed to HIV-infected blood or blood products, have the same risk of developing AIDS, say the authors, Janine Jason, MD, of the Center for Disease Control, Atlanta, and colleagues. The incidence and latency period of AIDS may not be the same for all risk groups due to different routes of infection and/or other possible cofactors. Knowing the answer to this question would be helpful in counseling infected persons, for understanding the natural history of HIV infections, and for devising ways to treat or prevent the spectrum of AIDS-related disease, the authors write.

Their study compared 79 HIV-infected men from a hemophilic treatment center in Pennsylvania with 117 homosexual men who had been treated for sexually transmitted diseases at a clinic in San Francisco. Serum samples documenting approximate dates of HIV infection were available for both groups. This information allowed the researchers to compare the incidence of AIDS among patients in both groups who have been infected for the same period of time. The overall incidence of AIDS did not differ significantly for the two groups (21 percent of the hemophilic and 27 percent of the homosexual men had developed AIDS), the authors report.

Although these findings are limited by the small size and geographically localized nature of the study populations, the authors suggest that the relative length of HIV infection, rather than the route of infection, is of primary importance in comparing disease outcome for different populations.

In an accompanying study, Lawrence D. Kaplan, MD, and colleagues at San Francisco General Hospital and other institutions, say the increased incidence of non-Hodgkin's lymphoma within the San Francisco population at risk for AIDS suggests that this lymph system cancer is the result of immune deficiency caused by HIV infection. Lymphomas in HIV-infected patients bear a striking resemblance to those seen in transplant patients receiving immunosuppressive drugs, they say.

The authors studied 84 patients with AIDS-associated non-Hodgkin's lymphoma who were treated with a variety of standard chemotherapeutic regimens. Patient's prognoses appeared to be related more directly to their underlying immunodeficiency state than to features of the lymphoma itself, they report. Survival was longer for patients who received "less aggressive" therapy, or with lower doses of the anticancer drug cyclophosphamide, which suggests that aggressive chemotherapy in this patient population may shorten survival by further suppressing the immune system.

Epstein-Barr virus (EBV), which causes infectious mononucleosis, is suspected of playing a role in the development of transplant-related non-Hodgkin's lymphoma the authors report. They say, however, that their failure to find EBV genetic sequences in 10 of the 15 lymphomas they studied raises doubts about the virus' causative role in AIDS-associated cases. They believe EBV is "merely a passenger virus rather than one that brings about malignant transformation."

In an accompanying commentary, Paul A. Volberding, MD, of San Francisco General Hospital, says the complexities of AIDS care are forcing the nation to reconsider its health care systems and to be prepared to revise them where needed to deal with the medical, psychosocial, and ethical problems of AIDS. Health professionals who care for AIDS patients assume a greater degree of responsibility and face a more complicated array of problems than in treating almost any other patient group. To continue to be effective, they must develop and implement strategies for their own psychological support, Volberding says. However, he says, stress-reduction groups for AIDS health care providers are seen as luxuries rather than as essential elements of our control of the epidemic. "AIDS poses *severe* and *chronic* stress for the health care provider and if we are to maintain our own health and continue to provide effective care, we *must* be provided with resources needed to reduce these stresses," he concludes.

JAMA February 3, 1989

OVERLY STRESSFUL RESIDENT TRAINING PROGRAMS MUST BE CHANGED: REPORT

Reform in hospital residency training programs is inevitable, and to avoid imposition of arbitrary restrictions, changes should come from within the programs themselves, say a report and editorial in the *Journal of the American Medical Association*.

Recent public concerns that overworked, fatigued residents are more likely to make life-threatening mistakes are being translated into legislation, say the authors of the report, John M. Colford, Jr, MD, and Stephen J. McPhee, MD, of the University of California, San Francisco.

"Sleep deprivation is probably the greatest source of stress in residency," they write. While the airline industry has recognized the dangers of sleep deprivation and has established guidelines to ensure that pilots receive adequate rest, hospital residents are expected to function for extended periods without sleep, they say. Residents also face considerable financial burdens, they write, noting that increasing educational debt and decreasing purchasing power of resident salaries has led to increased "moonlighting," which adds to fatigue and stress. Between 33 and 80 percent of residents are believe to moonlight, they report.

These stresses often lead to alcohol and drug abuse, broken relationships and divorces, anxiety, depression, and suicide among residents, the reports says. "Stress can also greatly affect resident's attitudes, professional behavior, and job satisfaction," they say. Pediatric interns studied had "more negative attitudes toward patients, worsened physician-patient relationships, and decreased positivity about life at the end of the internship year compared with the beginning," the authors report. "Residents may lose compassion for their patients—symbolized by the derogatory language that is sometimes used to refer to patients, eg, 'gomer' and 'dirtball'—and cynicism may result."

Other trends may force changes in training, the authors say. Fewer medical students are choosing internal medicine residencies, they say, and the shrinking applicant pool may force departments of medicine to make "concessions" on quality-of-life issues if they hope to continue to attract high-quality applicants.

While most physicians agree that the crisis requires changes in residency training programs, there is disagreement over what the changes should be, Colford and McPhee say. "The pace of change may accelerate once it becomes clear that society will no longer sanction and pay for the training of physicians in a way that may be dangerous to both the trainees and their patient." Fear of malpractice suits resulting from charges that residents work longer hours than is safe may speed up the process, they say. "One fact is clear: To avoid arbitrary restrictions imposed from without, residency programs must begin to make changes from within," they conclude. "It is the right thing to do; now is the right time to do it."

In an editorial, Timothy B. McCall, MD, of Cambridge, Mass., says "the public is outraged that life-and-death decisions are made by residents working 36-hour shifts and 100-hour weeks." While the medical community debates the merits of the present system, the public overwhelmingly disapproves of it and expects reform, he says. "The public believes that long working hours and sleep deprivation harm patient care. Hospitals that continue to overwork residents can expect lawsuits alleging that tired residents provided poor care. Teaching hospitals could pay multi-million dollar settlements." Residents are also demanding changes, as concerns about life-style increasingly leads talented individuals away from medicine, he says. "Even prestigious residency programs are having difficulty attracting qualified applicants."

Concrete, not just cosmetic, changes in working conditions are needed, McCall says—teaching stress-reduction techniques without actually reducing job stress won't work. Although inevitable, changes in residency training is being resisted by many in the medical establishment, he says. "Ideally, residency reform should come from the medical profession," he concludes. "If we fail to change residency training, it will be changed for us. There is no turning back."

JAMA February 10, 1989

AVERAGE DAILY BLOOD PRESSURE BEST PREDICTOR OF CARDIAC DAMAGE

Repeated blood pressure readings taken outside the doctor's office seem to be a much better way of predicting cardiac disease in hypertension patients than readings taken by a physician, a study in the *Journal of the American Medical Association* says.

Authors William B. White, MD, and colleagues at the University of Connecticut School of Medicine, Farmington, found patients whose blood pressure was higher only when taken in a doctor's office had heart size and function similar to that of patients with normal BP. "These

data support that it is the average blood pressure load over the day rather than the casual, physician blood pressure that determines the cardiac response in patients with hypertension," they write.

Elevated blood pressure seen only in a medical setting—"office" or "white coat" hypertension—affects perhaps 10 to 20 percent of mildly hypertensive persons in the United States, the report says. Thus, it has been unclear whether in-or out-of-office blood pressure is a better indicator of potential heart damage.

The authors studied three groups of age-matched, previously untreated subjects: "office" hypertensives—office BP over 140/90, awake ambulatory BP of 130/80 or less; "normals"—office BP 135/85 or less, ambulatory BP 130/80 or less; and "daytime" hypertensives—ambulatory BP over 140/90, office BP 140/90 or more. Cardiac size and function tests were then conducted; the "office" hypertensives had results similar to those seen in the normal individuals. Based on this, the authors say, "patients with office hypertension appear to be distinctly normal and separate from patients with borderline hypertension, who are often thought to be an intermediate population between normotension and hypertension."

"However," they note, "long-term follow-up of these patients is required to determine whether the incidence of vascular complications in patients with office hypertension differs from that of a comparable normotensive group."

JAMA February 10, 1989

PAP SMEAR SHORTFALLS CITED

While use of the Pap smear has greatly reduced morbidity and mortality rates from invasive cervical cancer, it also has resulted in "abysmal failures," says a report in the *Journal of the American Medical Association*. Leopold G. Koss, MD, of the Albert Einstein College of Medicine, Bronx, NY, says a lack of information, inadequate cervical cell samples and poor quality control measures are responsibility for many of the false-negative results in Pap smear testing. Approximately 10 to 20 percent of routine cervical smears are inadequate in some way, Koss says. He says laboratories should report such problems to those providing the sample as the first step "in ensuring laboratory performance." A series of reports has documented that "two cervical smears obtained simultaneously reduced the false-negative rate by at least 20 percent for precancerous lesions," Koss says. In addition, lab screenings should take at least five minutes and be limited to 50 screenings per technician per day to avoid fatigue, he says. Many of Koss' recommendations have been incorporated in the Federal Clinical Laboratory Improvements Act of 1988.

JAMA February 3, 1989

IRON DEFICIENCY IN HIGH SCHOOL SWIMMERS

Non-anemic iron deficiency is reported to be common in high school runners—especially girls—and may be related to repetitive exercise. Now, a study in February's *AJDC*, the *American Journal of Diseases of Children*, suggests non-anemic iron deficiency also is common in female high school swimmers, but does not seem to be due to swim training. Instead, say authors, Thomas W. Rowland, MD, and John F. Kelleher, MD, of the Baystate Medical Center, Springfield, Mass., poor dietary intake of iron and menstrual blood flow seem to be key contributors. The study looked at serum ferritin levels in 30 high school swimmers at the beginning and end of a competitive swim season. Iron depletion was initially present in nearly half the girls, although none had evidence of impaired red blood cell production. No significant changes were seen over the course of the season. However, the authors say, "dietary intake of iron was poor, particularly in the girls, in whom it averaged 43 percent of the recommended dietary allowance." In addition, "menstrual histories suggested an inverse relationship between the amount of menstrual flow and the serum ferritin level," they say.

LONG-TERM COSMETIC RESULTS IN CONSERVATIVE BREAST CANCER SURGERY

The vast majority of women who undergo conservative surgery ("lumpectomy") combined with radiation therapy for early-stage breast cancer have excellent long-term cosmetic results, a study in February's *Archives of Surgery* reports. The study, by Mary Ann Rose, MD, now with St. Anne's Hospital, Fall River, Mass., and colleagues, reviewed the records of 593 breast cancer patients treated between 1968 and 1981, scoring breast appearance as excellent, good, fair or poor. Ninety percent had a good or excellent results after three years, say the authors. What's more, they say, these results appear stable over time—of 36 patients assessable at seven years follow-up who had good or excellent cosmetic scores after three, 94 percent still had a good or excellent result. Tumor size and chemotherapy use affected cosmetic outcome. "Our results provide support for the use of breast-conserving treatment by demonstrating satisfactory cosmetic results that appear to remain stable over time," the authors conclude.

EATING AFFECTS BLOOD PRESSURE IN ELDERLY, HEMODYNAMICS IN HEART PATIENTS

A report in February's *Archives of Internal Medicine* says eating a meal can result in a drop in blood pressure that might be a factor in fainting and falls in some elderly patients. The study, by Steven J. Peitzman, MD, and

Stanley R. Berger of the Medical College of Pennsylvania, Philadelphia, involved 16 people all over age 75, who were active, healthy, free of cardiovascular disease and taking no blood pressure medication. Seated and standing blood pressure and heart rate were measured in each study subject before and after eating a standard breakfast and before and after drinking a volume of water (as a control). Eight persons under age 50 also underwent similar measurements after eating the meal. The elderly but not the young study subjects showed a significant drop in blood pressure after eating, "with heart rate increases in some subjects clearly inadequate for the decline in systemic pressure," the authors say. Although no ill effects were seen in the elderly subjects studied, this after-eating blood pressure drop "may in some less robust elderly persons be a factor in (fainting) and falls," they say. "This change may also confuse the monitoring of antihypertensive treatment in older outpatient."

COMPARING CIGARETTE DEPENDENCE WITH ALCOHOL OR DRUG DEPENDENCE

Cigarette dependence seems to be at least as "addictive" as other drug use but not as pleasurable, says a study in the *Journal of the American Medical Association*. The report, by Lynn T. Kozlowski, PhD, of the Clinical Institute Addiction Research Foundation, Toronto, and colleagues, asked some 1,000 people seeking alcohol or drug treatment to gauge, relative to cigarettes, how hard it would be to kick their substance abuse problem, their strongest urges to use the substance, and the pleasure it gave them. Fifty-seven percent said cigarettes would be

harder to give up than their problem substance. Those dependent on alcohol were about four times more likely than those dependent on other drugs to say their strongest urges for cigarettes were at least as great as those for their problem substance. Cigarettes also were generally rated as less pleasurable than alcohol or other drugs. They study "testifies powerfully to the 'addictiveness' of cigarettes," the authors say.

JAMA February 10, 1989

ELECTRICAL STIMULATION FOR BONE FRACTURES

Non-invasive electrical stimulation is a safe form of adjunctive treatment for stable non-united bone fractures (those that don't heal on their own), an AMA science study panel concludes, but the panel is divided over the technique's effectiveness. The Diagnostic and Therapeutic Technology Assessment (DATTA) panel's report, published in the *Journal of the American Medical Association*, says 69 percent of 29 expert panel members polled considered electrical stimulation established as safe for non-united fractures; 21 percent called it investigational and 10 percent indeterminate. But on the issue of effectiveness, 36 percent considered the technique established, 39 percent called it investigational, 21 percent indeterminate, and 4 percent unacceptable. Electricity has been used to heal bone lesions since 1812, the report notes, but many panel members believed "the lack of controlled clinical trials compromised a thorough evaluation of the effectiveness of the treatment."

JAMA February 10, 1989



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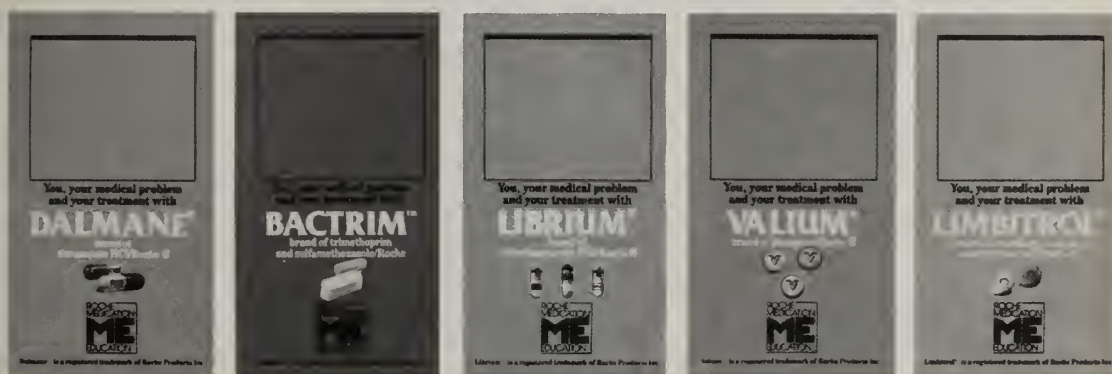


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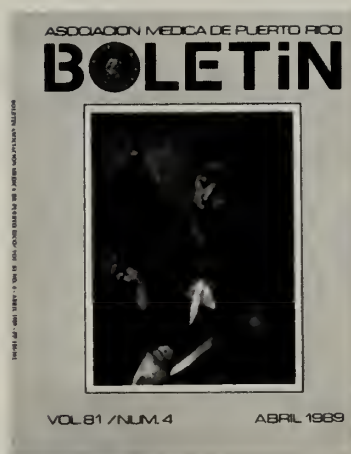
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Nuestra Portada

Osiris Delgado nació en Humacao el 1 de abril de 1920. Se graduó de Bachillerato en Artes de la Universidad de Puerto Rico en 1951. Estudió en academias e institutos de Arte en Italia, Francia y España. En 1954 obtuvo el grado de Doctor en Filosofía y Letras de la Universidad Central de Madrid.

Se desempeñó como profesor de arte en la Universidad de Puerto Rico en Río Piedras. Ha sido Presidente de la Sección de Bellas Artes del Ateneo Puertorriqueño y Director del Museo de la Universidad de Puerto Rico.

Entre otros ha publicado los siguientes trabajos de crítica: "Luis Paret y Alcázar; Pintor Español;" "Picasso Ante su Obra" y "Proyecto para la Conservación del San Juan Antiguo." Entre sus cuadros se distinguen: "La Suerte de la Cuerda" y "Cántico a Santiago de las Mujeres." Es autor de una "Sinopsis Histórica de las Artes Plásticas en Puerto Rico" (1957).

En 1966 pinta su obra "Cosiendo" en la que la tenue llama de un quinqué en el lado izquierdo de la composición ilumina la figura de la niña, que con gran delicadeza cose la bandera en un gesto simbólico de solidaridad social apartando su quehacer para el engrandecimiento de su patria.

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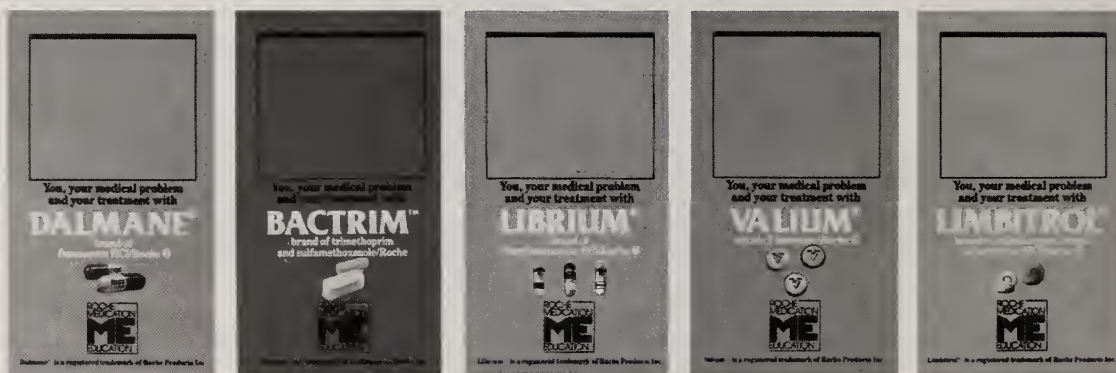


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ESTUDIOS CLINICOS

Función Pulmonar en Atletas Puertorriqueños de Alto Rendimiento

Walter R. Frontera MD, PhD*

Erick Suárez, PhD*

José R. Rodríguez Santana, MD**

Pedro Mayol MD**

Arturo Córdova, MD***

Resumen: El perfil fisiológico del atleta de alto rendimiento ilustra las adaptaciones que el entrenamiento prolongado y la influencia genética pueden producir en el cuerpo humano. Las pruebas de función pulmonar son parte de dicho perfil y han sido utilizadas para evaluar el estado de salud y el nivel de aptitud física de los deportistas. En este trabajo se describen algunas variables de función pulmonar en atletas puertorriqueños de alto rendimiento. La población fue estratificada tomando en consideración las características técnicas y metabólicas de los diferentes deportes. Utilizando la clasificación técnica, el análisis estadístico revela que solo el grupo deportivo de coordinación y arte competitivo (deportes como gimnasia, velas, tiro) tiene valores significativamente menores para las variables FVC/estatura ($P=0.003$) y FEV_1 ($p=0.014$). Dichas diferencias desaparecen al clasificar los deportes de acuerdo a las demandas energéticas en aeróbico, anaeróbico o combinado. Estos resultados sugieren que las clasificaciones deportivas actuales no distinguen atletas por diferencias en la función pulmonar en reposo. Es posible que las variables analizadas en este estudio no sean buenos indicadores del estado de entrenamiento de estos atletas.

La fisiología del atleta de alto rendimiento ("elite") ha sido, en las últimas décadas, tema de gran interés para la comunidad científica. En particular, muchos investigadores han estudiado las respuestas y adaptaciones que la exposición repetida y frecuente a sesiones de ejercicio puede producir a largo plazo en el cuerpo humano. Tres factores principales se combinan para producir adaptaciones morfológicas y funcionales al entrenamiento en varios órganos y sistemas del cuerpo: el

genotipo, las influencias ambientales (incluyendo el entrenamiento y la nutrición), y el control genético sobre la sensibilidad del cuerpo humano para adaptarse. El análisis de las adaptaciones al entrenamiento deportivo, evidente tanto en el estado de reposo como durante el ejercicio, permite entender un organismo que ha optimizado su función y que es capaz de ejecutar cerca de los *límites máximos fisiológicos* del rendimiento humano. No es sorprendente por lo tanto, que sea de gran interés el estudio del perfil fisiológico del atleta de alto rendimiento.

Uno de los componentes de un perfil fisiológico es la función pulmonar (FP). Las pruebas de FP han sido utilizadas por varios investigadores para evaluar el estado de salud de los atletas,¹ caracterizar las respuestas fisiológicas al ejercicio,² y estudiar los efectos del entrenamiento sobre el cuerpo humano.³ La importancia de la FP radica en el hecho de que la ventilación representa el primer eslabón en la cadena de transporte de oxígeno; un sistema fisiológico vital en diversos tipos de ejercicios y actividades deportivas. Cambios en la FP de naturaleza obstructiva y/o restrictiva no solo afectan la salud de la persona sino que también pueden limitar el rendimiento del atleta.

Los propósitos de este estudio fueron: 1) evaluar una muestra de la población puertorriqueña de atletas de alto rendimiento; 2) describir estadísticamente, tomando en consideración la edad, el sexo, la estatura y el peso, las siguientes variables de función pulmonar: capacidad vital forzada (FVC), FVC corregido por la estatura ($FVC\ est^{-1}$), FVC corregido por el peso ($FVC\ peso^{-1}$), volumen expirado al primer segundo (FEV_1) de una espiración forzada máxima, y la razón entre FVC y FEV_1 ($FEV_1\ %$); 3) comparar estadísticamente dichas variables por grupos de atletas cuyos programas de entrenamiento se caracterizan por diversas demandas técnicas y metabólicas; 4) determinar la correlación estadística entre las variables estudiadas.

Nos interesa contestar las siguientes preguntas: 1) ¿existen diferencias en las variables de función pulmonar entre los diferentes grupos deportivos?; 2) ¿si existen, cómo se afectan estas diferencias de acuerdo a las características técnicas y metabólicas utilizadas tradicionalmente para clasificar los deportes?

*Centro de Salud Deportiva y Ciencias del Ejercicio del Albergue Olímpico, Comité Olímpico de Puerto Rico y Recinto de Ciencias Médicas, Universidad de Puerto Rico.

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Materiales y Métodos

Sujetos Un total de 203 atletas pre-seleccionados para representar a Puerto Rico en los X Juegos Panamericanos de 1987 en Indianápolis (Indiana - E.U.A.) fueron evaluados. Dichos atletas representaron un total de 21 deportes.

Características Generales. La edad, el sexo, el peso y la estatura fueron las características generales estudiadas. El peso y la estatura fueron medidos con una balanza Detecto.

Variables de Función Pulmonar. Los atletas asistieron a una clínica de evaluación pre-competencia donde se utilizó un sistema de varias estaciones para evaluar su estado de salud. Se establecieron tres estaciones para las medidas de función pulmonar en cuartos separados con aire acondicionado. Tres terapeutas respiratorios entrenados y con experiencia en pruebas de función pulmonar realizaron las medidas utilizando los siguientes instrumentos: un espirómetro sellado con agua de 13.5 litros (Collins, Braintree, Mass), un espirómetro seco (Pulmonaire 10, Jones Medical Instrument Co., Oakbrook, IL) y un espirómetro manual de volumen (Spirometric Inc, Auburn, Me.).

Cada atleta realizó la prueba un mínimo de tres (3) veces recibiendo estímulo verbal durante la misma. Los resultados fueron evaluados por tres (3) especialistas en neumología. De no ser aceptables, la prueba fue repetida hasta obtener resultados adecuados. Las siguientes variables fueron estudiadas: FVC, FVCest⁻¹, FVCpeso⁻¹ FEV₁ y FEV₁%.¹

Clasificación por Grupo Deportivo. Los deportes fueron agrupados de acuerdo a sus características básicas (tabla I) siguiendo la clasificación de Lanier⁴. En adición (tabla II) los deportes fueron divididos de acuerdo a la fuente de energía predominante durante el proceso de entrenamiento⁵ en: predominantemente (>60% de la energía se obtiene de este sistema) aeróbico (PA), predominantemente anaeróbico (PAn) y combinado (Co.).

Análisis Estadístico. Para determinar la distribución estadística de cada variable cuantitativa, se calcularon el promedio y la desviación estándar.⁶ El estudio de las diferencias entre los promedios de grupos y sexos, controlando la edad, la estatura y el peso, se hizo con la técnica de análisis de covarianza (ANCOVA). Para identificar las diferencias significativas entre grupos, comparamos la variabilidad de modelo con y sin la presencia de un determinado grupo. Utilizamos la prueba de Bartlett para verificar la homogeneidad de varianzas, condición necesaria para el uso de ANCOVA. En ausencia de homogeneidad las variables correspondientes fueron transformadas utilizando la función raíz cuadrada. En caso de no lograrse la homogeneidad de varianzas con la transformación, utilizamos la prueba no paramétrica de Kruskal - Wallis. Finalmente la asociación entre las variables estudiadas se determinó con el coeficiente de correlación de Pearson. Un valor de $p < 0.05$ fue definido como estadísticamente significativo. Para el almacenamiento de datos se utilizó el paquete EPIINFO.⁷ El análisis estadístico se realizó utilizando el paquete de computación Statistical Package for the Social Sciences SPSS-X.⁸

Resultados

Características generales. Según las tablas I y II el 33.5% y el 76.8% de los atletas participaron en juegos con pelota y en deportes PAn respectivamente. La tabla III presenta el promedio de edad, estatura y peso para la población estudiada según el sexo.

Un análisis estadístico más detallado se realizó agrupando los deportes según las tablas I y II. Utilizando la clasificación de la tabla I (por grupo técnico) encontra-

Tabla I

Clasificación por Grupo Técnico*		
Grupo N	Características Técnicas de los Diferentes Deportes	Ejemplos de Deportes
1 (R) M=25 F=13	Resistencia	atletismo (>,800 metros) ciclismo de ruta, remos
2 (FR) M=12 F=3	Fuerza rápida y velocidad	atletismo (saltos, velocidad y lanzamiento), levantamiento de pesos
3 (C) M=35 F=6	Combate	boxeo, judo, esgrima, lucha olímpica
4 (P) M=49 F=19	Juegos con pelota	baloncesto, beisbol, voleibol, tenis, polo acuático
5 (AC) M=27 F=14	Coordinación y Arte Competitivo	gimnasia, velas, tiro, clavados, equitación

* adaptado de referencia 4.

N: número de atletas en el grupo por sexo.

Tabla II

Clasificación de Deportes de Acuerdo a las Demandas Metabólicas*		
Grupo N	Sistema Metabólico Predominante	Ejemplares de Deportes
1 (PA) M=16 F=5	Aeróbico	ciclismo de ruta, carrera > de 1,500 metros, natación (>400 metros)
2 (PAn) M=108 F=48	Anaeróbico	carrera 100 metros, lucha olímpica, levantamiento de peso, tenis, beisbol
3 (Co) M=24 F=2	Combinado	boxeo, carrera de 800 metros, natación (200 metros)

*adaptado de referencia 5.

N: número de atletas en el grupo por sexo.

Tabla III

Características Generales ($\bar{x} \pm s.d.$)			
Sexo (N)	Edad (años)	Estatura (cm)	Peso (kg)
M (148)	24.9 \pm 7.0	173.8 \pm 9.1	74.6 \pm 14.9
F (55)	21.2 \pm 6.6	158.6 \pm 8.9	56.1 \pm 11.9

mos una interacción estadísticamente significativa entre el sexo y el grupo para la edad ($p=0.02$); la estatura ($p=0.009$) y el peso ($p=0.024$). En otras palabras, la magnitud de la diferencia entre los promedios de los grupos depende del sexo (o viceversa). El análisis individual para cada sexo reflejó que en el sexo masculino hubo diferencias significativas entre grupos para las variables edad ($p=0.001$), estatura ($p=0.015$), y peso ($p=0.017$). El grupo 5 resultó ser mayor, el grupo 4 resultó ser el más alto y los grupos 2 y 4 los de mayor peso.

Por el contrario, en el sexo femenino no hubo diferencias entre grupos para la edad ($p>0.05$), pero sí para la estatura ($p=0.001$) y el peso ($p=0.048$). En el caso de la estatura, los grupos 3 y 5 resultaron ser significativamente más bajos y en cuanto a la variable peso los grupos 2 y 4 significativamente más pesados.

Según la clasificación de la tabla II (por demandas metabólicas) no hubo diferencias significativas entre grupos ($p>0.05$) ni entre sexos ($p=0.201$) para la variable edad. En el caso de la estatura y el peso los varones resultaron ser más altos ($p<0.001$) y pesados ($p<0.002$). La diferencia entre los sexos fue independiente del grupo.

Variables de función pulmonar. Las tablas IV y V presentan los resultados para las variables de función pulmonar según la clasificación deportiva y el sexo. Según la tabla IV el FVC fue mayor en atletas de sexo masculino ($p=0.002$). Las diferencias entre los grupos no fueron significativas ($p=0.058$). El modelo de covarianza, donde se toma en consideración la edad, la estatura y el peso explicó el 64.3% de la variación (%VEM) del FVC. En otras palabras, el 35.7% de la variación en el FVC fue el resultado de otros factores diferentes de la edad, la

Tabla IV

Variables de Función Pulmonar en Grupos Clasificados por Demandas Técnicas									
Grupo (N)	\bar{X} (FVC) (L)			\bar{X} (FVC $\text{est}^{-1} \times 100$) (L cm^{-1})			\bar{X} (FEV ₁) (L)		
	M	F	Total	M	F	Total	M	F	Total
1 [R] (38)	5.03	3.83	4.62	2.89	2.34	2.69	4.22	3.60	4.00
2 [FR] (15)	4.90	3.59	4.64	2.78	2.15	2.65	4.16	3.13	3.95
3 [C] (41)	4.66	3.42	4.48	2.71	2.31	2.65	3.90	3.03	3.77
4 [P] (68)	5.04	3.71	4.67	2.84	2.31	2.69	4.10	3.12	3.83
5 [A] (41)	4.46	3.02	3.97	2.61	1.95	2.38+	3.76	2.66	3.39+
Total	4.83*	3.53	4.48	2.77*	2.22	2.62	4.02*	3.10	3.76
o		0.60			0.36			0.56	
%VEM		64.3%			43.8%			49.8%	

o = Estimación del error estándar.

% VEM = Porcentaje de variación explicado por el modelo de covarianza.

* = $p<0.05$ con respecto al sexo femenino

+ = $p<0.05$ con respecto a otros grupos

Tabla V

Variables de Función Pulmonar en Grupos Clasificados de Acuerdo a las Demandas Metabólicas†									
Grupo (N)	\bar{X} (FVC) (L)			\bar{X} (FVC $\text{est}^{-1} \times 100$) (L cm^{-1})			\bar{X} (FEV ₁) (L)		
	M	F	Total	M	F	Total	M	F	Total
1 [PA] (21)	4.80	3.70	4.54	2.78	2.28	2.65	4.11	3.24	3.90
2 [PAn] (156)	4.87	3.52	4.45	2.79	2.22	2.62	4.02	3.11	3.74
3 [Co] (26)	4.68	3.24	4.57	2.69	2.01	2.64	3.95	2.70	3.85
Total	4.83*	3.53	4.48	2.77*	2.22	2.62	4.02*	3.10	3.77
o		0.020			0.37			0.57	
%VEM		64.9%			40.6%			45.5%	

† Debido a diferencias significativas en la variabilidad presentada en cada grupo y sexo (prueba de homogeneidad de varianzas) las variables FVC y FVC est^{-1} fueron transformadas utilizando la función raíz cuadrada.

o = Estimación del error estándar.

% VEM = Porcentaje de variación explicado por el modelo de covarianza.

* = $p<0.05$ con respecto al sexo femenino.

estatura y el peso. La corrección del FVC por la estatura (FVC_{est}^{-1}) fue menor en el grupo 5 ($p=0.003$) y en el sexo femenino ($p<0.001$) en ausencia de interacción. El porcentaje de variación en la variable FVC_{est}^{-1} explicado por el modelo de covarianza fue 43.8%.

La corrección del FVC por el peso (FVC_{peso}^{-1}) reflejó una diferencia significativa entre grupos ($p=0.001$) pero no entre sexos ($p>0.05$). El grupo 1 se comportó estadísticamente diferente ($p<0.001$) con respecto a los demás grupos. Los promedios para el FVC_{peso}^{-1} fueron: grupo 1 = 7.3 ± 0.9 ; grupo 2 = 6.0 ± 1.2 ; grupo 3 = 6.7 ± 1.6 ; grupo 4 = 6.5 ± 1.1 ; grupo 5 = 6.1 ± 1.1 .

El análisis del FEV_1 demostró diferencias significativas entre sexos ($p=0.004$) y grupos ($p=0.014$) en ausencia de interacción. El FEV_1 fue mayor en personas de sexo masculino y menor en el grupo 5. El modelo de covarianza explicó 49.8% de la variación. No hubo diferencias entre sexos o grupos para la variable $FEV_1\%$ (masculino 83.2 ± 6.0 ; femenino = 85.4 ± 5.2).

El análisis estadístico de los resultados según la clasificación por demandas metabólicas (tabla V) reveló diferencias significativas entre los sexos, pero no entre los grupos para las variables FVC ($p=0.004$), FVC_{est}^{-1} ($p=0.001$), y FEV_1 ($p=0.012$). No hubo diferencia significativa entre los sexos pero sí entre los grupos ($p=0.006$) para el FVC_{peso}^{-1} ; siendo este menor en el grupo 2 (PAN). Bajo esta clasificación, el modelo de covarianza explicó 64.9% y 45.5% de la variación en el FVC y el FEV_1 respectivamente. Al igual que en la clasificación por grupo técnico no hubo diferencias entre sexos o grupos para la variable $FEV_1\%$.

Asociación entre variables: Una correlación significativa fuerte fue evidente entre la estatura ($r=0.76$; $p<0.001$), el peso ($r=0.62$; $p<0.001$) y el FVC. De igual forma la correlación entre el FVC y el FEV_1 ($r=0.87$; $p<0.001$) fue altamente significativa.

Discusión

Características generales. Las diferencias encontradas en las características generales son de esperarse tomando en consideración la heterogeneidad deportiva de la población estudiada. Los grupos deportivos incluyen atletas adolescentes de gimnasia (edad promedio = 16.3 años) y adultos de edad media (promedio = 40.4 años) en los deportes de tiro y escopeta. Varios investigadores han demostrado la variabilidad en las características antropométricas tales como el peso, el porcentaje de grasa, el somatotipo y la estatura⁹ en diversas poblaciones atléticas. Dicha variabilidad se relaciona en cierto grado con las características técnicas, tácticas y reglamentarias de cada deporte. Por ejemplo en el deporte de gimnasia, el peso corporal debe ser bajo puesto que el atleta lo sostiene en diversos movimientos con las extremidades superiores. De igual forma, en las carreras de larga distancia, el gasto energético aumentará con un incremento en el peso del cuerpo. Por el contrario, en los deportes de lucha olímpica, judo y boxeo es necesario un peso corporal alto en las categorías pesadas. En el caso de la estatura, es evidente la ventaja que ofrece en el baloncesto y el voleibol; no así en la gimnasia.

Variables de función pulmonar. Los valores promedios obtenidos en este estudio para las variables FVC, FEV_1 y $FEV_1\%$ en el sexo femenino son similares a los publicados por Crapo y colaboradores¹⁰ para la población general de edad y estatura comparable, pero más bajos que los informados por Miller¹¹ para la población general y De-Meersman y Schitz¹² y Clanton y colaboradores¹³ en atletas de similar edad y estatura. Por otro lado, nuestra población del sexo masculino demostró unos valores promedio de FVC y FEV_1 menores que los informados por Crapo y colaboradores¹⁰ y Miller¹¹ para la población general. Al evaluar estos resultados es importante señalar que no hay una correlación entre el rendimiento deportivo y la capacidad vital pulmonar.^{14, 15, 16} Más aún, no se ha demostrado inequívocamente que los valores estáticos de función pulmonar como la capacidad vital y los dinámicos como el FEV_1 aumentan con el entrenamiento.^{13, 14, 15}

En términos generales, los volúmenes pulmonares son mayores en el sexo masculino y en personas de estatura alta.¹⁰ Nuestros resultados están de acuerdo con estas observaciones como lo ilustran las diferencias significativas entre sexos (tabla IV y V) y la correlación entre el FVC y la estatura. Sin embargo, es interesante señalar que aún tomando en consideración la edad, la estatura y el peso, solo podemos explicar 64.3% de la variabilidad en el FVC y 49.8% de la variabilidad en FEV_1 . Otro factor que puede influenciar significativamente dicha variabilidad es la fortaleza de los músculos ventilatorios; característica fisiológica del músculo esquelético susceptible al estímulo del entrenamiento deportivo.^{15, 16}

Las tablas de clasificación utilizadas en este estudio son un instrumento tradicional para agrupar los deportes que demuestran tener similitudes en términos de la estructura del entrenamiento deportivo. En nuestro análisis vemos que, en términos de las variables de FP, son muy pocas las diferencias significativas encontradas. Más aún, es importante señalar que las diferencias entre los grupos para las variables de FP según la clasificación por grupo técnico (tabla IV), desaparecen al reagruparlos atletas de acuerdo a las demandas metabólicas (tabla V). Estos hallazgos reflejan una pobre relación entre las variables estudiadas de FP y las demandas técnicas y metabólicas de los grupos deportivos según se clasifican en la actualidad y nos sugieren que las pruebas de FP, aunque puedan ser utilizadas para la evaluación del estado de salud de los atletas, no son de utilidad para distinguir entre los diferentes grupos estudiados. Para estudiar más a fondo esta problemática, sugerimos realizar un estudio donde, partiendo de la distribución de frecuencias de los valores de una serie de variables fisiológicas, desarrollemos una nueva clasificación. En otras palabras, el punto de partida serían las variables y no la clasificación.

Agradecimiento

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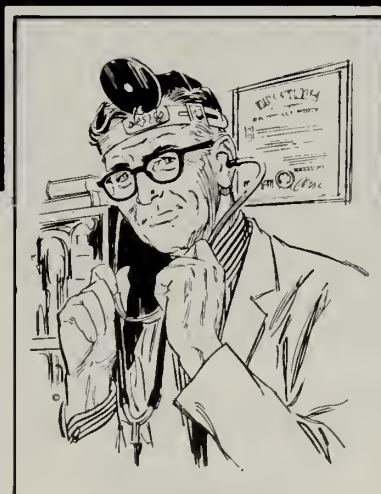
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Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

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Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

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OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

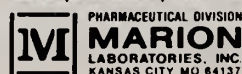
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Reference:

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Acido Desoxirribonucleico (DNA) en Pruebas de Filiación, Paternidad y Medicina Forense

Adolfo Pérez-Comas, MD, PhD*

La constitución genética de un individuo está determinada por la secuencia de bases en el ácido desoxirribonucleico (DNA) celular. Unidades y segmentos específicos de éste constituyen los llamados genes que determinan las características individuales y familiares de un sujeto.

En la última década, se han desarrollado técnicas en genética que permiten fraccionar y estudiar regiones detalladas del DNA, permitiendo caracterizar las mismas para su empleo como marcadores específicos familiares e individuales.¹⁻³

La discriminación alcanzada con la técnica del DNA, sobrepasa por mucho la de otros marcadores convencionales como HLA, grupos serológicos, proteínas y enzimas sanguíneas. Representa en este momento la forma más certera de análisis de caracteres individuales de sujetos con fines de identificación y filiación. Es la prueba que permite establecer quien es y quien no es el padre.

Su utilidad es amplia en casos civiles de filiación y paternidad, al igual que en casos criminales donde muestras de semen, sangre, pelo, etc., pudieran ser estudiadas.⁴⁻⁷

Acido Desoxirribonucleico

El DNA constituye nuestro material hereditario. Su estructura viene determinada por dos cadenas dispuestas en forma helicoidal a la manera de una escalera con sus peldaños. Los peldaños estarían constituidos por las bases adenina, timina, guanina y citosina. Las mismas se aparean siempre en combinación adenina-timina o guanina-citosina en distintas secuencias u orden que determinan grupos de unidades que constituyen, en forma simple, los genes.

Si en un lado de la cadena hay citosina, en el otro lado siempre habrá guanina, lo mismo ocurrirá con la combinación adenina-timina. Dicha secuencia se repetirá millones de veces en cada individuo, dando lugar a los caracteres únicos de cada individuo.

En miles de lugares la cadena de DNA presenta secuencias similares de bases. Dichos fragmentos se conocen como "secuencias repetitivas", constituyendo fragmentos de DNA sin función aparente alguna. Representan puntos o paradas muertas del código genético, variando en su longitud y número en cada individuo. Estudiando

dichos fragmentos, podemos identificar sujetos con inconfundibles marcadores que bien podrían llamarse huellas de material genético, con implicaciones similares a las huellas digitales de un sujeto.

Fundamento de la prueba

La complementación de bases en ambas cadenas nos permite identificar las bases presentes en otro sujeto siempre y cuando tengamos una cadena de DNA cuya secuencia de bases (estructura primaria) nos sea conocida.

La disposición espacial (estructura terciaria) del DNA en forma helicoidal vendrá determinada por la presencia de pares de bases específicos donde la adenina se apareará únicamente con timina, y la citosina con guanina. Ello dará lugar a lo que se conoce como secuencia palindrómica de DNA, es decir - la secuencia de las bases en una cadena será el inverso de su cadena par como se observa aquí.

Figura 1. Apareamiento de Bases en el DNA.

A = adenina
T = timina
G = guanina
C = citosina

```

  --- A A G C T T ---
  --- T T C G A A ---
  
```

cadena 1
cadena 2

Diversas técnicas bioenzimáticas permiten emplear las llamadas enzimas de restricción para fragmentar el DNA en diferentes segmentos que posteriormente son separados mediante electroforesis para estudio. Estos fragmentos pueden ser transferidos a material de nilón para análisis, mediante una técnica conocida como "Southern blotting" (impregnado Southern) llamada así en honor a su inventor el Prof. E. Southern.

Muchos de estos fragmentos contienen secuencias repetitivas, las cuales pueden ser purificadas y posteriormente marcadas con isótopos radioactivos para poder así detectar su presencia.

Los fragmentos de secuencias repetitivas marcadas con radioisótopos se conocen con el nombre de "probes". Dichos "probes" se hibridizan (se unen) a los fragmentos separados por el gel.

Así, si nosotros juntamos una secuencia A obtenida con la técnica de Southern a una secuencia complementaria B (nuestro "probe" de DNA de estructura conocida) bajo unas condiciones específicas, tendrá lugar la hibridización con su pareja de bases. La misma podrá ser identificada al exponer la membrana de nilón a una

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placa fotográfica donde la radioactividad dará lugar a una imágenes en bandas en la fotografía, de disposición similar al código de barras que indican el precio en múltiples productos.

La constitución cromosómica de un individuo viene condicionada por la de ambos padres. Lo mismo ocurre con las áreas de restricción y los diversos fragmentos.

En el proceso de formación de óvulos y espermatozoides ocurre un rearreglo del DNA, pero a la misma vez muchas secciones se mantienen inalteradas. El hijo o la hija heredará caracteres de DNA de ambos padres, constituyendo la combinación un individuo único.

Cuando se analiza el DNA con la técnica de secuencias repetitivas, se detectan fragmentos de origen paterno, de origen materno y otros específicos al niño.

Las bandas obtenidas permiten derivar el origen paterno o materno de las mismas. Con ello se logran amplios estudios genéticos en casos de enfermedades hereditarias (algunas distrofias musculares, corea de Huntington, enfermedad fibroquística del páncreas, y algunas hemoglobinopatías), en casos de filiación y paternidad, en violaciones y asesinatos para la identificación de individuos y en problemas migratorios.^{1-8, 11-13}

Hay diversas técnicas de estudios de fragmentos de DNA, clasificándose las mismas en las de locus simple, que estudian una sola región, y la de locus múltiple desarrollada por el Prof. A. Jeffreys de la Universidad de Leicester en Inglaterra.¹⁻²

Los estudios de locus simple permiten analizar un fragmento de un cromosoma, dando lugar a un patrón de una a dos bandas en la placa fotográfica. Ello limita su uso para casos de paternidad donde se requieren estudios más detallados. La posibilidad de que ocurra una mutación lo limita aún más, ya que daría lugar, con toda probabilidad, a falsas interpretaciones.

Con la técnica de locus múltiple, de las cuales la única disponible comercialmente es la del Prof. Jeffreys, los "Jeffreys Probes" patentados por el Instituto Lister de Medicina Preventiva y los Laboratorios Cellmark de Inglaterra, se obvia la posibilidad de error de juicio por mutación al estudiarse varias regiones, evidenciándose de cuarenta y cinco a sesenta segmentos (bandas) diferentes de DNA, variando el número según los individuos. La técnica detecta múltiples segmentos de DNA localizados en muchos cromosomas. El tamaño y la densidad de las bandas es variable, además de específicas para los individuos, siendo nominadas por el Prof. Jeffreys como "huellas de DNA".

Cada "probe" mostrará de veinte a treinta bandas distintas, permitiendo utilizar de cuarenta y cinco a sesenta bandas diferentes para comparar entre individuos. Las bandas de cada "probe" serán distintas unas de las otras, al representar segmentos diferentes. Con ello podría observarse la presencia de una mutación en un fragmento, pero no en el otro fragmento.

Técnica de estudio

Bastará con una pequeña muestra de sangre, semen, pelo, o cualquier material biológico que contenga células de DNA.

Se procesan con técnicas bioenzimáticas que emplean

endonucleasas de restricción para cortar las cadenas dobles del DNA en fragmentos específicos. Mediante electroforesis se separan los fragmentos de DNA, desplazándose los mas pequeños en forma mas rápida que los pesados. Los mismos se separan en el gel en forma de bandas invisibles.

Se transfieren las bandas (que incluyen fragmentos repetitivos de DNA y otros fragmentos) a una banda de nilón. Se tratan con "probes de DNA de Jeffreys" marcados con radioisótopos. Estos últimos se fijan a las bandas invisibles específicas de DNA repetitivo de la muestra desconocida según sea su secuencia de bases.

Un placa fotográfica se sensibiliza por los fragmentos repetitivos que fijaron la cadena desconocida, dando lugar a las "huellas de DNA" para dicho sujeto. Este patrón de bandas es específico para cada persona (a excepción de gemelos idénticos), permitiendo además obtener información sobre los padres, ya que la mitad del DNA se hereda del padre y la otra mitad de la madre. Ello permite su empleo en casos de filiación y paternidad en disputa.

Manejo adecuado de la muestra

En los casos civiles y criminales habrá de asegurarse una seria, estricta y confiable cadena de custodia en la obtención, manejo y procesamiento de las muestras. En gran medida, de ello dependerá el servicio que esta técnica de a la justicia.

Habrà de requerirse que las personas envueltas se personen a la misma vez para la toma de muestra por un profesional calificado. Los sujetos a analizar servirán en la identificación el uno del otro, evitándose así que terceras personas comparezcan con identificaciones falsas. Además deberá estar presente un testigo que certifique la toma de las muestras.

Una vez tomada cada muestra se identificará el tubo con el nombre de la persona, fecha y hora, y no antes del procedimiento ya que podría inducir errores. Todos los tubos deberán ser colocados en un envase especial y sellado con la firma del flebotomista. Se colocan en una bolsa plástica y se sellan nuevamente. Se colocan junto con la documentación del caso en una caja especial, la cual se envía sellada al laboratorio de investigación que procesará las muestras. El laboratorio verificará el estado de las muestras a su recibo, y continuará con la custodia de las mismas hasta que se obtengan los resultados finales.

La documentación del caso incluirá nombre y dirección de los sujetos, edad, y raza. Vendrá acompañada por fotografías firmadas de los sujetos o en su defecto de sus huellas digitales del dedo gordo. Nosotros preferimos realizar una fotografía conjunta de las personas a quien se les extrae la muestra, para documentar su presencia e identificación simultánea, a la vez que tomamos también las huellas digitales.

Una vez obtenidos los resultados se redacta un informe con un análisis del caso en particular, enviándose copia a las partes interesadas (Tribunal, y los representantes legales del padre en disputa, y la madre e hijo/a). En nuestro Instituto, bajo ninguna circunstancia, el informe será privativo de una de las partes.

Comparación con otros métodos

La técnica de estudio del DNA con fragmentos múltiples constituye el único método disponible comercialmente que permite establecer quien es y quien no es el padre de un sujeto. Su elevado grado de discriminación solo puede verse afectado en el caso de dos gemelos idénticos que se vean acusados como presuntos padres. Su capacidad discriminativa es de 1 en 30 billones. Si tomamos en cuenta que la población mundial es de aproximadamente 5 billones, de los cuales apenas 2.5 billones son hombres (y aproximadamente un tercio de ellos no son adultos), nos damos cuenta de su elevado grado de exactitud.

Mediante las técnicas de HLA aisladas se obtiene un probabilidad de inclusión - exclusión de aproximadamente 95%, los cual implicaría que en P.R. podría haber cerca de 7000 personas con el mismo haplotipo. Si sumamos a dicha prueba otros marcadores como los ABO, subgrupos Rh, MNSs, Kell, Duffy, proteínas y enzimas séricas, elevaremos la probabilidad a un 98-99% aproximadamente, lo cual constituye una cifra que queda muy por debajo de lo que provee la técnica del DNA con locus múltiple.

Si comparamos las pruebas convencionales de paternidad con la técnica de DNA de locus múltiple encontramos:

Figura 2. Métodos Convencionales vs. Técnica Multi-Locus DNA en Paternidad

Pruebas Convencionales	Técnica de Multi-Locus DNA
63-99% Exclusión	Exclusión de Hombres Falsamente Acusados
Probabilidad de paternidad 99% basada en cálculo estadístico.	Establece si ES o NO ES el padre.
Resultados varían con raza, y otros factores.	Resultados no dependen de otros factores externos.
Para algunas pruebas el niño debe de ser mayor de 6 meses.	No hay límite de edad.
Prueba debe de comenzarse antes de pasadas las 72 hrs. de extraída la sangre.	No hay límite de tiempo.
Con frecuencia se requiere más de una prueba.	Solo requiere una sola determinación.

La técnica de locus múltiples constituye al presente, la mejor prueba de identificación de sujetos, comparada a la identificación de huellas digitales con el nombre de Huellas de DNA. Permite la identificación positiva de sujetos envueltos en casos de paternidad, crímenes, desastres naturales, niños perdidos, y en casos de inmigración adonde se discute la relación familiar del inmigrante. Permite además realizar estudios mas detallados de enfermedades hereditarias, seguimiento de transplantes y estudios investigativos de cultivos celulares, además de su empleo en el establecimiento de linaje en caballos, perros, peces, aves y otros animales.⁹⁻¹⁵

Su utilidad ha sido recogida por múltiples publicaciones médicas y legales,^{16, 22} habiéndose resuelto casos en las cortes europeas y norteamericanas con el empleo de esta técnica.

Su uso y empleo debe limitarse a profesionales entrenados en el campo de la genética médica que puedan determinar la presencia de mutaciones, implicaciones familiares y cálculos bioestadísticos.

Su disponibilidad en nuestras manos nos lleva a recomendar a nuestros Tribunales, los jueces, fiscales y abogados en general de Puerto Rico a hacerse conscientes de las bondades e implicaciones científicas de las pruebas de DNA en locus múltiple, y la administración de la justicia en casos de filiación y paternidad. Su aplicación en otros casos forenses también debe ser recalçada.

Summary: A new precise method of personal identification with significant implications for civil and criminal paternity cases, as well as for other forensic purposes and genetic studies is presented.

DNA multi-locus analysis offers a discrimination of 1 in 30 billions, constituting the most precise determination in paternity testing. If we consider that the world population is around 5 billion people, and that less than 2.5 billions are males, of the which approximately 1/3 are not adults, then we can see how the possibility of error is extremely low. It makes other paternity studies with HLA, blood groups, enzymes and proteins ineffective in paternity disputes.

All courts and legal personnel should be aware of the scientific implications of this new available test in our media.

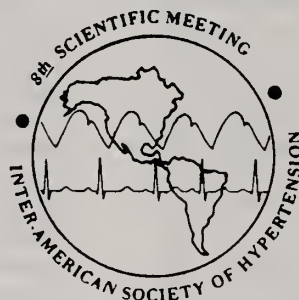
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VIII SCIENTIFIC MEETING INTER-AMERICAN SOCIETY OF HYPERTENSION



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UNDER THE AUSPICES OF:

The Inter-American Society of Hypertension

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IN COOPERATION WITH:

University of Puerto Rico School of Medicine

GENERAL INFORMATION

DATE: May 13 - 17, 1989

SITE: Caribe Hilton International Hotel,
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SATELLITE SYMPOSIA

Satellite symposia are also planned.

May 13 (Sat). - 17 (Wed.), 1989
SAN JUAN, PUERTO RICO

IMPORTANT DATES

Deadline for receipt of abstracts November 21, 1988
Notification of Abstract acceptance January 30, 1989
Deadline for pre-registration March 15, 1989

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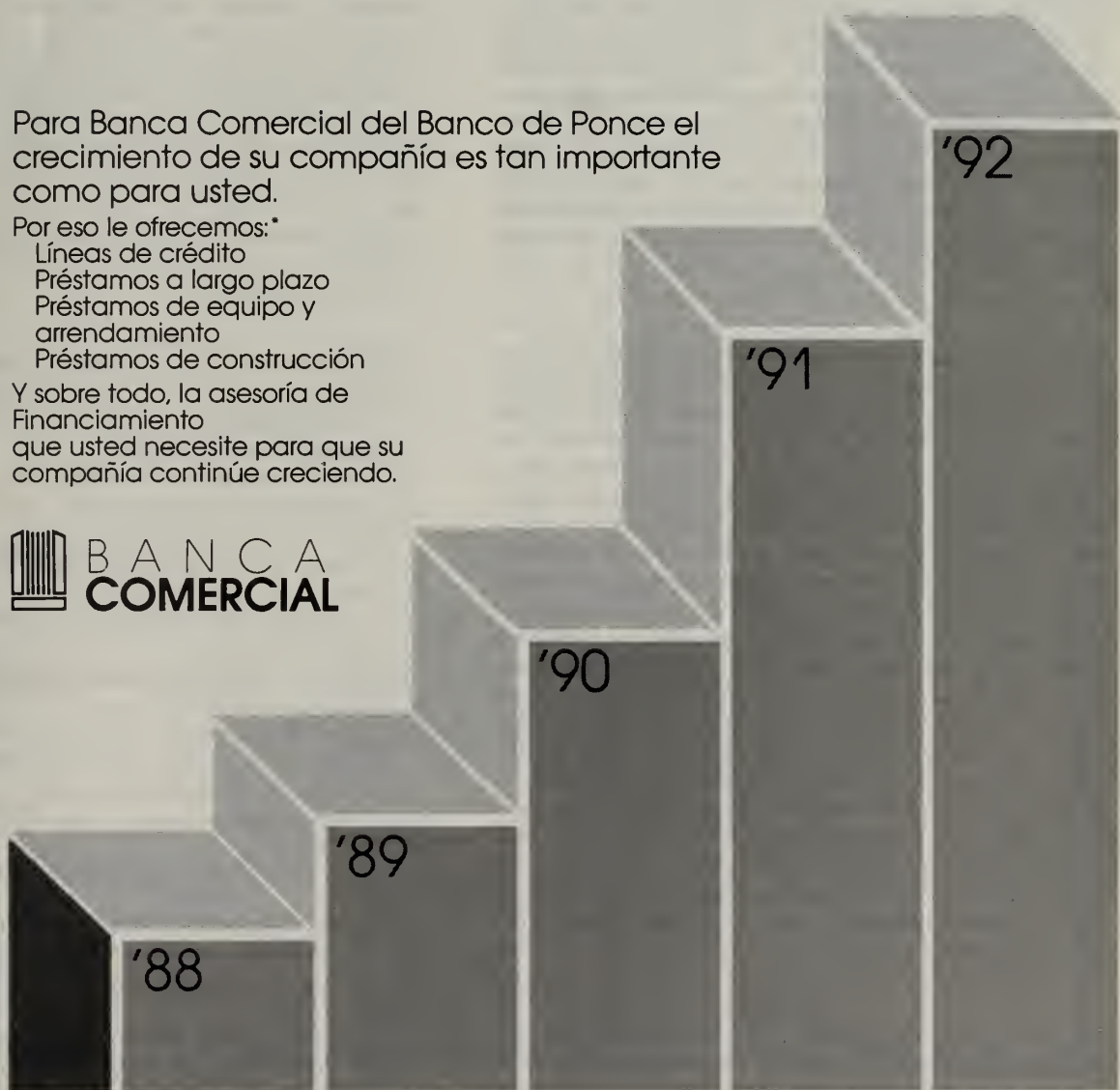
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A Naturalistic Analytic Study of Veterans Using Naltrexone in Puerto Rico

Erick F. Santos, MD

Summary: Clinical records of eighteen patients on Naltrexone and 13 patients who dropped out of a Naltrexone maintenance activity were studied at random to delineate the biopsychosocial characteristics of greater clinical relevance to an outpatient rehabilitation program. Their similarities and differences were described. Some hypothesis that may prove to be great clinical benefit were presented. A striking finding was the greater capacity of the Naltrexone group to have a stable marital relationship ($P < 0.01$) as compared with the group who abandoned treatment.

Dependence on opiates is considered a mental disorder according to the diagnostic and statistical manual of the American Psychiatric Association. The people suffering from this disorder tend to spend most of their time looking for these drugs or for means of obtaining it causing great suffering to their families and to their capacity to achieve adequate and productive roles within society. Generally these persons are affected by other psychiatric disorders that add additional stresses upon their lives already plagued by social pressures and dangerous situations. However these external pressures are usually the motivators to bring them to treatment programs that promote their emotional growth, the values compatible with a drug free life and the behavior necessary to prevent relapses. Naltrexone Hydrochloride, a long acting pure opiate antagonist, is a powerful agent that serves to prevent relapses, to maintain abstinence and to promote attendance to psychotherapeutic activities. To better understand why some these patients benefit from Naltrexone hydrochloride while others do not the author decided to examine and compare the characteristics of both groups.

Methodology

The purpose of this naturalistic analytic study is to compare and delineate some important clinical characteristics of these patients and to propose new hypothesis that might be useful to develop future clinical studies. These patients are a special group of opiate dependent veterans because of their willingness to use Naltrexone an oral long acting opiate receptors blocker as a tool to enhance their rehabilitation opportunities. The criteria

for selection was open and we did not deny the Naltrexone to a veteran even when this veteran was not considered to have a good prognosis (unmarried, poor working and academic skills, severe mental illness, inadequate supportive network).¹ Our null's hypothesis is that there are no significant differences in between these two groups of Drug Dependent Veterans. Patients who remain using Naltrexone versus patients who have abandoned its use.

The following variables were studied according to our experience and to the current literature to confirm or reject this hypothesis:

1. Age³
2. Previous time in the clinic to their initiation on Naltrexone.
3. Working status⁴
4. Present academic studies.
5. Stable heterosexual relationships⁵
6. Parental involvement.
 - a. Yes - No
7. Average G.A.S. score (Goal Attainment Scale Score)⁶
8. Psychiatric disorders present (D.S.M. III AXIS I criteria was used).
9. Service connected status for psychiatric condition.
10. Relapses motives.
11. Sexual Performance or desire for sexual activity.
 - a. Intense - At least once every day.
 - b. Strong - At least three times per week.
 - c. Fair - At least once a week but less than 3 times a week.
 - d. Poor - Less than once a week.

Our clinical experience and current literature guided us into the selection of these variables which hold great promises in elucidating useful keys to improve treatment strategies.²

In order to develop new hypothesis for further studies in these field we utilized the chisquare: A non-parametric statistic technique, appropriate to the nominal and ordinal data to be obtained and the small numbers of subjects involved in this study.

A comparison of the results on the patients who stay in the rehabilitation program using Naltrexone with those who abandoned the program was made.

The Goal Attainment Scale evaluation technique was used to measure the biopsychosocial progress of patients.⁶

The D.S.M. III criteria were used to determine the AXIS I psychiatric disorders present in these patients (life time prevalence).

The records of 13 patients who discontinued the use of Naltrexone were examined a month later. The results of both groups were compared to delineate the similarities and differences of both groups. All available records were studied on both groups.

Both groups of patients received the usual outpatient methadone free psychotherapeutic multimodal treatment at the San Juan V.A. Hospital Drug Dependence Treatment Clinic.

Results

Comparison of Patients Active on Naltrexone Group A Versus Patients who Abandoned This Treatment Group B

Variable	Group A (N=18)	Group B (N=13)
1. Previous time in the program	a. 91 days=56% (10) b. 31 to 90 days=0% (0) c. 30 days=44% (8)	77% (10) 08% (1) 15% (2)
2. Working at time study	44% (8)	46% (6)
3. Studying at time study	17% (3)	0% (0)
4. Stable Heterosexual Marital relationship	89% (16)	54% (7)
5. Parents involved actively in treatment Program	39% (7)	31% (4)
6. Average age of Patients	33.8	35.4
7. Average Goal Attainment Scale (50 and over means and adequate biopsychosocial functioning)	Initial=40.3 At 3 months=57.3 At 6 months=59.1 At 9 months=67.2 At 12 months=72.8	31 47 44 — —
8. D.S.M. III Disorders:		
a. D.S.M. III Axis I		
Affective Disorder	61% (11)	61% (8)
b. Dysthymic Disorders	28% (7)	38% (5)
c. Schizophrenia	22% (4)	23% (3)
d. Cyclothymic Disorder	11% (2)	0
e. Manic Depressive Disorder	6% (1)	0
f. Major Depressive Disorder	6% (1)	23% (3)
9. Service Connected Status:		
S.C.	33% (6)	38% (5)
N.S.C.	67% (12)	61% (8)
10. Relapses Motives		
a. To continue the use to Heroin	9 (100%)	8 (73%)
b. To use alcohol	0	2 (18%)
c. To use Cocaine	0	1 (9%)
d. Unknown		2 (18%)
11. Sexual Performance	Group A (N=13)	Group B
a. After 2 weeks of Trexan use	Intense=6 Strong=6 Fair=1	Data either not reliable or not available
b. Sexual performance before Trexan use	Intense=0 Strong=0 Fair=6 Poor=7	

Discussion

The comparison between the group (N=18) who stayed in Naltrexone (Group A), at the time of the study May 1986, versus the group who decided to discontinued the

opiate antagonist (N=13), (Group B) showed the following:

The Group B had a large number of patients who were old clients (more than 3 months) of the clinic, difficult patients, very resistant to our therapeutic suggestions (77%). It had only 23% of patients with less than 3 months of previous contacts with the clinic. Group A showed a large number of patients with less than 3 months of previous contacts with the clinic (33%). All these percents were highly significant on Chisquare analysis ($P < .01$), meaning that many new patients were attached to the clinic by the new modality of treatment. In both groups close to 45% of the patients were working at the time of the study.

Three patients in Group A (Those on Naltrexone) 17%, were studying. No patients in Group B (Those who abandoned Naltrexone) were studying. Suggestive of some difference in aspirations and social functioning. In Group A, 16 (89% of the 18 patients had a stable heterosexual relationship. This finding was significant to more than $P < .01$ level. In Group B, 7 (54%) had a stable heterosexual relationship this was an expected value in our society. Parents involvement was 39% in Group A and 31% in Group B, and the average age for Group A was 33.8 years and Group B was 35.2 years, very similar results for both groups.

The Goal Attainment Score showed a higher initial score in Group A (40.3) vs. Group B score (31). At 3 months of therapy the patients of both groups who stayed in treatment showed a similar increase in score (around 16 units). However, by six months in therapy the Group A patients G.A.S. score was 59.1. The Group B score of 23% (3 of 13) of patients still receiving the Naltrexone for over 3 months was only 44 units, even lower than at the third month measure 47. Group B patients never achieved an average score of 50 in the Goal Attainment Scale which means an inadequate Biopsychosocial functioning. The patients of Group A had accumulated an average of 6.46 months of treatment. Group B patients tended to drop out of treatment during the first month of therapy; 10 of 13 patients (77%). These facts reflected in Group B greater involvement with the Heroin and other drugs and less family support. A 92% of the Group A patients showed on the sexual performance variable a strong to intense response. This finding was coupled with an increase interest in his family. Data from Group B was not reliable.

In regard to psychiatric disorders, life time prevalence using the D.S.M. III criteria, 61% of both groups showed affective illnesses predominating the dysthymic disorder (approximately 38% on both groups). Schizophrenia appeared on 22.6% of the join data of both groups, significantly higher than in the general population. Both groups showed a similar composition of Service Connected, (A=33%, B=38%) vs. Non-Service Connected patients (A=67%, B=62%). The reasons for the relapses of Group A patient were always related to the continued use of Heroin. In Group B only 73% admitted the same reason, 33.33% mentioned that the use and desire to use other drugs was the main reason, (Alcohol and Cocaine).

The patients who stayed on Naltrexone and the regular therapeutic program of the clinic (Group A) tended to be

new clinic patients. Those who failed to stay (Group B) tended to be old patients of the clinic and very resistant to abstinence.

Both groups were similar in regard to age, working status, parental involvement in treatment, psychopathology (D.S.M. III AXIS I) medication side effects during the first week and the percentage of service connected vs. non-service connected patients. These facts showed that we were dealing with a population that was very similar in composition. This fact makes us think that the observed differences should prove to be very useful to psychoterapists in their rehabilitation mission.

In Group A patients stable heterosexual relationships predominate with a high degree of significance ($P < 0.01$) over Group B patients. Group A patients then should have greater capacities to relate to women in intimate relationships. They were more patient and able to reach agreements with other human beings than Group B patient as observed clinically. The Goal Attainment Scale on the initiation of the Naltrexone Treatment. Group B patients tended to drop out of treatment early, usually within the first month. This fact appears to be evidence of their ambivalence and pessimistic outlook toward the future.

Naltrexone was a powerful agent in restoring the sexual desire and performance in the Group A patients. Data from Group B patients was not reliable and absent in many records.

Both groups showed significant higher percentage of psychiatric conditions than the general population specially Dysthymic and Schizophrenia Disorder.

Other significant findings were the lack of family involvement in the treatment program ($P < .01$) on both groups which seems to indicate lack of faith and affective withdrawal of relatives probably related to the chronicity, frequent relapses, the social stigma, the antisocial behavior and the economical losses related to these patients mental and behavioral disorders. The gradual and significant improvement of Group A patients in their Biopsychosocial functioning as measured by the Goal Attainment Scale. This reflects their greater ability to obtain family, therapeutic and community support contrasting with most of the patients who dropped out of the Naltrexone maintenance activity who did so within the first month of treatment (77%). This seems to indicate that their motivation to function free of drugs was not very strong. Finally in our study the most powerful positive correlate with treatment acceptance and improvement was a stable Heterosexual relationship.

Conclusions

Both groups of veterans were similar in regard to age, working status, parental involvement in treatment, psychopathology and service connected status. However the patients showing the better outcome were associated with greater numbers of marital unions, higher global biopsychosocial functioning, more and better communication with therapists and higher preference for opiates with less attraction to other types of dependence inducing drugs.

Naltrexone Hydrochloride tend to restore the sexual interest and improve the sexual performance of former opiate dependent patients. A future study could probably clarify the permanence of these changes as well as their importance in the rehabilitation of the patients.

In general patients need to realize the importance of keeping their marital unions intact or to strive to develop this kind of bond. Also the need to relate to therapists as much as possible to have more and better support and to improve their biopsychosocial strength.

These patients also should be educated regarding the importance of achieving abstinence of other non-prescribed psychotropic substances, notably alcohol, Cocaine and Cannabis, if they want to be successful in achieving a good outcome on their rehabilitation efforts.

The above conclusions indicate the presence of a combination of biopsychosocial factors in the etiology and persistence of this illness. The preventive and therapeutic tools should therefore, include biological and psychosocial strategies on the individual, its family members and society in general. The teaching of mental health principles, psychosocial skills, interpersonal skills, communication skills, problem solving skills and good social values seems to be essential for the prevention and treatment of this illness. On the biological side also the capacity to treat mental disorders should be present in the Drug Abuse Treatment Centers; it is a must to assure complete evaluations and comprehensive interventions that will then facilitate the rehabilitation of the patients.

Resumen: Los records médicos de 18 pacientes que estaban usando Naltrexona y 13 pacientes que abandonaron esta actividad terapéutica fueron estudiados al azar, para determinar aquellas características biosociosociales de mayor utilidad clínica en un programa de rehabilitación ambulatoria. Se descubrieron sus similitudes y diferencias. Algunas hipótesis fueron presentadas ya que prometen ser de gran utilidad clínica.

Un hallazgo de gran relevancia clínica ($P < 0.01$) fue la mayor capacidad del grupo que se mantenía usando Naltrexona para mantener una relación marital que la del grupo que abandonó el uso del antagonista del opiáceo.

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REVIEW ARTICLES

Computer Eyestrain

Manuel N. Miranda, MD
Sixto García Castiñeiras, MD, PhD
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Summary: Main ocular mechanisms probably underlying eyestrain symptoms in computer users—diminished aqueous tears, extraocular muscle fatigue, color fatigue and decreased amplitude of accommodation induced by monochromatic light—are discussed. With this background, some practical consequences are drawn to avoid or reduce eyestrain.

Most surveys indicate that people who work with computers for prolonged periods of time complain of eyestrain symptoms more often than control groups. The most frequent symptoms are redness, dryness and tiredness of the eyes, increased lacrimation, blurred or double vision, fixation difficulties, periorbital pain and headaches.¹⁻⁶

These problems appear to derive from the obligatory interaction of the user with the television-like screen of the computer or computer terminal, also called the video display terminal (VDT), the monitor, the video display unit (VDU) or the cathode ray tube (CRT).

Relative to printed material characters in the VDT are relatively blurred, may have appreciable flicker² and their luminance is variable.⁴ On the other hand, the screen has to be observed at a relatively close range and in the horizontal or near horizontal viewing plane. These and other factors may adversely influence people who work with computers for prolonged hours without rest. What we consider the main mechanisms of ocular origin probably underlying eyestrain symptoms are discussed in this paper. Other sources of computer related hazards or concerns are not considered here although they may also have important health implications, like those related to prolonged exposure to low levels of radiation, body posture and workplace environment conditions.⁵⁻⁷

Tear Production

Working with a VDT may induce in some people a tendency to stare at the screen, reducing the frequency of

spontaneous blinking. Eyelid movement is of critical importance for the continued renewal and regeneration of the precorneal tear film, which provides the cornea with the proper physiological environment.⁸ Reduced blinking results in increased evaporation of the aqueous layer of the tear film, leading to the sensation of dryness and irritation experienced by the VDT operator.

Extraocular Muscles Fatigue

During regular reading, the position of the optical axis is from about 30 to 45° down from the horizontal plane and inward, thus favoring the relaxation of all the extraocular muscles except for the superior obliques. When the eyes move inward, the superior oblique muscle depresses the globes. However, the effort made by the contraction of the oblique muscles tends to be minimized by the fact that they work with the force of gravity in depressing the eyes and their action is mediated through a long tendon and pulley mechanism that multiplies the force exerted.

On the contrary, working before computer screens generally puts the optical axis at the level of the horizontal plane or just below it. To keep the eyes in this position—equivalent to the primary position of the eyes—all the six extraocular muscles must contract. If the effort has to be sustained for hours, muscular strain is likely to occur. It has been established that when sustained muscular force exceeds 10 or 15% of the muscles capacity, fatigue develops.⁹

Color Fatigue

The fact that color fatigue develops after working before a computer screen is documented by reports of "prolonged complementary chromatopsia" in VDT operators.^{10, 11} This is the name given to a reversible condition in which objects known to be white appear tinted after the use of VDTs. Pink vision (erythropsia) develops after the use of monochrome green screens, and green vision (chloropsia) follows the use of red VDTs. In all cases reported the persons affected had otherwise normal color vision. Prolonged complementary chromatopsia has been described in about 10% of VDT users.¹¹ The condition appears to be related to the well known phenomena of color fatigue and afterimage formation.^{10, 12} If one stares at a colored image painted or

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projected onto a white surface for a minute or so the color becomes desaturated and tends to fade away. This is because the main retinal photoreceptors for that particular color cannot regenerate their photosensitive pigment fast enough to maintain an steady output of electrical signals to the brain (color fatigue).

Once the retina has developed color fatigue, if one directs the sight towards the white background, the original image can be seen again but tinted now with the complementary color (afterimage effect).

Amplitude of Accommodation

Accommodation is probably best described as the result of an oscillating mechanism produced by the ciliary muscle which searches for the retinal image of highest contrast.¹³ We have discussed in a previous work the influence of illumination and chromatic factors on the amplitude of accommodation.¹⁴

Of particular relevance now is our finding that the best stimulus for accommodation was polychromatic, white light. Green light produced 12% less accommodative power. Red and specially blue light were clearly less effective (35% and 85%, respectively) in eliciting the accommodative response of white light. The effectiveness of blue light as stimulus for accommodation significantly increased by increasing the level of illumination of the target, a finding which may also be of considerable importance for the comfortable operation of computer monitors.

The close range of viewing demanded from computer screens requires accommodation to be sustained for prolonged periods of time. This is partially compensated by the fact that the mean age of computer operators is relatively low and therefore we are dealing with a population of good amplitude of accommodation. However, if characters on the screen are displayed with monochromatic lights - with the potential exception of green - strain of the accommodation mechanism may indeed result after prolonged periods of time of exposure to the screen. On the other hand, blurred, flickering characters will baffle the oscillating mechanism of accommodation, which is unable to produce an image of highest contrast in the retina.

Conclusion

We have presented what we believe are the most important sources of eyestrain for the VDT operator or any person working with computers for long hours. How biochemical phenomena (depletion of photosensitive pigments, excessive muscle activity) may lead to the feeling of fatigue is essentially unknown and should remain the object of active investigation. Some immediate practical consequences, however, result from the previous discussion. Eye irritation due to decreased blinking can be counteracted with the use of ophthalmic wetting drops. Care should be taken not to work too close to the screen. The monitor should be properly placed so that the eyes are looking downward. Avoid reflections on the screen and do not work against backgrounds with high illumination. Introduce frequent periods of rest and let the eyes focus on distant objects. All these precautions

will lead to higher contrasts on the screen and to relaxation of the extraocular muscles and those involved in accommodation. Other practical aspects have to do with the design of the computer screen. Efforts should be directed towards the production of stable characters of high contrast with the least amount possible of flicker. Preference to screen colors eliciting highest accommodation response should be given. Our results appear to indicate that these are black and white or green screens. For some persons, however, green screens may lead to disturbed color perception after prolonged hours of use.

Resumen: Se discuten en este trabajo los mecanismos oculares probablemente mas importantes de los síntomas de astenopia en usuarios de computadoras: reducción del volumen de la secreción lacrimal, fatiga de los músculos extraoculares, fatiga al color y reducción de la amplitud de acomodación inducida por la luz monocromática. Sobre esta base se derivan algunas reglas prácticas para evitar o reducir la astenopia.

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CASE REPORT

Unusual Trauma to Spinal Cord: Case Presentation

Nathan Rifkinson, MD
Eric Carro, MD

A thirty year old woman was sitting on the beach in a bathing suit one sunny day, enjoying the company of her friends, when a sudden strong gust of wind lifted a nearby large beach umbrella hurtling it toward the small group of people. There was a sudden sharp cry from the woman as her friends quickly dispersed, trying to avoid the flying umbrella and sand. But the woman remained sitting, unable to move her lower extremities.

Her friends returned and lifted the young woman into their car and brought her to the emergency room of our Medical Center.



Artist's Concept of Occurrence

Examination revealed a deep one centimeter laceration in the posterior portion of the right deltoid. There was a sensory loss from T8 down and a flaccid paraplegia. X-rays of the thoracic spine revealed an intraspinal, two centimeter notched metallic object at the T8-T9 level.

At surgery this metallic object was found intraspinally, anterolaterally, but extradurally. There was no evidence of laminal fracture.



Figure 1. AP view shows tip of umbrella ray at T8-T9.

When examined last, eighteen months after her injury, there had been a return of the position sense of the large toes and some return of flexion at the hips bilaterally. Sensation in all modalities had returned "spotilly". She had discarded her Foley catheter and voided well except for slight difficulty in starting her stream.

In attempting to explain the mode of these events, it is most probable that one of the rays of the umbrella pierced the patient's deltoid at high velocity, tore a thin tract subcutaneously through the posterior chest muscles, entered the spinal canal through the ligamentum flavum, and the umbrella continued its flight uninterrupted,

being carried away by the fierce wind and leaving the notched metallic object trapped intraspinaly. The object, when extracted, fitted the tip of the naked umbrella ray and was identical to the other protective tips on the remaining seven. The entire event lasted no more than five seconds.



Figure 2. Lateral view showing tip of umbrella ray in spinal canal.

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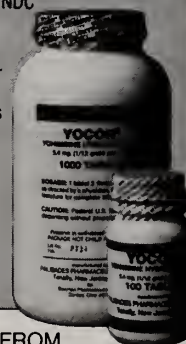
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ARTICULOS ESPECIALES

Educación Médica en Puerto Rico: Un Reclamo a la Excelencia

Raúl A. Marcial-Rojas, MD, JD*

La ausencia de una política pública certera, definida, consistente y consecuente ha caracterizado al desarrollo de la educación médica en Puerto Rico, particularmente durante los últimos quince a veinte años. Esta falla ha sido en gran medida el resultado de numerosas, noveles y variables situaciones que durante dichos años han surgido con relación a la educación médica, al ejercicio de la profesión médica y a la prestación de los servicios de cuidado médico. Lamentablemente, en la mayoría de las veces las autoridades pertinentes van respondiendo a presión de grupos, a situaciones resultantes de la pobreza o ausente planificación previa, o a conceptos equivocados de buena fe donde resalta la insuficiencia de datos confiables que respalden la racionalidad de la toma de decisiones.

No es el objeto de esta comunicación la discusión y análisis de los factores y situaciones arriba expresados, pero pudiera serlo en una ocasión ulterior. Motiva nuestra participación al presente sendos artículos publicados en esta revista por dos distinguidos educadores médicos. El primer artículo por el Dr. E. Vázquez-Quintana¹ y el segundo por el Dr. José Ramírez Rivera.²

El artículo más reciente² termina con las siguientes recomendaciones que se copian directamente sin siquiera traducirlas al español: "I would like to echo Dr. Vázquez-Quintana's suggestions in this manner:

1. A medical school open in Mayaguez (but sponsored by the University of Puerto Rico).

2. The three threatened residency programs in Caguas, Ponce and Mayaguez should intimately be associated with Liaison Committee accredited medical schools.

3. The Educational Consortium of Medical Education of the University of Puerto Rico and the Department of Health should join hands so as to provide salaries and fringe benefits appropriate to entice interested physicians

in continuing a career as educators in the Regional Teaching Hospitals of Puerto Rico.

4. The accreditation as internships of clerkships in facilities not nationally accredited for medical education should be withdrawn.

Even those with limited foresight and narrow vision must see the light darkening at the end of the educational tunnel. A sponsor to correct our misguided trajectory in medical education is requested now."

Es nuestro propósito abordar y analizar a continuación dichas recomendaciones en la misma secuencia en que han sido expresadas en la cita anterior.

I. Una Nueva Escuela de Medicina en Mayaguez

Ambos colegas^{1, 2} desempolvan un informe rendido por la Fundación Carnegie en 1970 donde se le recomendaba al Gobierno de Puerto Rico que auspiciara una segunda escuela de medicina pública en el Recinto Universitario de Mayagüez. A esta recomendación no accedió la Universidad de Puerto Rico. Debemos recordar que para dicha época, específicamente 1968, el Congreso de los Estados Unidos aprobó el Health Manpower Act que autorizaba fondos federales para la construcción de nuevas escuelas de medicina y para la ampliación de las ya existentes bajo la percepción que el país adolecía de una escasez de personal médico. Se recomendaba la incrementación de la producción de dichos profesionales médicos ante las perspectivas de que la accesibilidad al cuidado médico bajo la Gran Sociedad del Presidente Johnson sería muy mejorada.

A la sazón se condujeron estudios por el sector privado. La Fundación Carnegie en el 1970 y la Fundación Macy en 1976 rindieron informes separados que coincidían en que era urgente aumentar el número de médicos. Desafortunadamente, como ocurre en tantos de los programas de nuestra sociedad pluralística, no existía una planificación adecuada a largo plazo. Es ya por todos conocido el informe de 1980 de la Administración del Presidente Carter, ordenado por su Secretario de Salud Joseph Califano al Graduate Medical Education National Advisory Committee (GMENAC), donde se concluyó

Decano Facultad de Medicina y Presidente Universidad Central del Caribe.

**Solicitar sobretiros al autor en Call Box 60-327, Bayamón, Puerto Rico 00621-6032*

que el país tendría un exceso de 70,000 médicos para el 1990 como resultado del enorme crecimiento en escuelas de medicina nuevas y de la ampliación de las ya existentes en la década del 1970. Recientemente Alvin Tarlov, quien dirigió el GMENAC y al presente preside la Henry J. Kaiser Family Foundation, revisó y actualizó los hallazgos del informe original concluyendo que prácticamente todas las conclusiones fueron reafirmadas.³

La Universidad de Puerto Rico no compró la idea de crear otra escuela de medicina en Mayagüez, pero en dicha década (1970) incrementó sus admisiones de 60 a 150 estudiantes de medicina. Esto era equivalente, con referencia a la producción de médicos, a la creación de otra escuela de medicina, probablemente a un costo menor para el Gobierno de Puerto Rico. No es menos cierto que dicho incremento de matrícula trajo consigo numerosos problemas para la institución y sus programas los cuales no son pertinentes a esta comunicación.

Aún asumiendo, para el propósito de argumentar, que la recomendación de establecer una segunda escuela de medicina pública en el Recinto Universitario de Mayagüez hubiese tenido validez en el 1970, no podemos menos que concluir que los dos distinguidos colegas inciden en sus respectivas recomendaciones de crear la misma al presente dentro de la realidad histórica del país: (1) existen al presente dos nuevas escuelas de medicina privadas debidamente acreditadas por el Comité de Enlace en Educación Médica (LCME) y otra tercera acreditada únicamente por el Consejo de Educación Superior (CES); (2) la Escuela de Medicina de la Universidad de Puerto Rico se encuentra en estos momentos en el proceso de reducir el número de admisiones progresivamente.

Comprendo perfectamente bien que el Dr. Vázquez Quintana, de la mejor buena fe, recomendara en su artículo el establecer una escuela de medicina privada en Mayagüez. También, que taxativamente mencionara como tal a la Escuela de Medicina de Bayamón, la cual al momento de publicar su artículo luchaba por una licencia de autorización para iniciar operaciones de parte del Consejo de Educación Superior y de la que él fungía como asesor de su Junta de Síndicos. No veo nada reprochable en eso, el deseo de lograr hacer algo más y autorealizarse es muy genuino.

El Dr. Ramírez Rivera tiene un inmenso cariño por los programas graduados médicos del Centro Médico de Mayagüez y fue director del Consorcio Educativo de la Escuela de Medicina en dicho Centro Médico del 1976 al 1982. Recomienda el Dr. Ramírez una segunda escuela de medicina pública en Mayagüez. Sus motivaciones son también sinceras y genuinas.

Creemos, sin embargo, que no existe justificación alguna para recomendar la creación de otra escuela de medicina, pública o privada, en Puerto Rico al día de hoy y con toda probabilidad tampoco en el futuro predecible. Fundamentamos esta aseveración en abundante data pertinente disponible, que no es posible incluir por limitación de espacio, pero que es bien conocida por los numerosos estudiosos de este tópico y por las agencias acreditadoras concernidas. El salvar los programas médicos post graduados de Mayagüez es importante y abordaremos dicho tema mas adelante.

II. Programas de Residencia en los Hospitales de Caguas, Ponce y Mayagüez

El Dr. Ramírez Rivera se refiere en su artículo a los programas médicos post graduados que operan en los hospitales del Departamento de Salud en Caguas, Ponce y Mayagüez que pudieran estar en peligro de perder su acreditación por el Accreditation Council on Graduate Medical Education (ACGME) y recomienda que debieran dichos programas estar íntimamente asociados con escuelas de medicina acreditadas por el LCME.

Yo comparto la preocupación expresada por el Dr. Ramírez Rivera y abundaré sobre dicho tema mas adelante cuando elaboremos sobre los programas de internado y residencia en Puerto Rico. Sin embargo, debo señalar que en dichos tres hospitales al presente operan consorcios educativos de la Escuela de Medicina de la Universidad de Puerto Rico; por lo cual debemos inferir que dichos consorcios educativos a nivel subgraduado no han tenido impacto beneficioso significativo en la calidad de los programas postgraduados en dichos hospitales.

III. El Consorcio Educativo Médico entre la Universidad de Puerto Rico y el Departamento de Salud

Entiende El Dr. Ramírez Rivera que el Gobierno de Puerto Rico (U.P.R. y Departamento de Salud) deben juntos proveer sueldos y beneficios marginales apropiados para lograr reclutar y retener médicos que deseen desarrollarse como educadores en dichos consorcios. La idea es una buena en cuanto al incremento de recursos, pero la distribución de los mismos, las instituciones a utilizarlos, y las prioridades y metas a lograrse ameritan un análisis ponderado a luz de la realidad histórica presente de Puerto Rico. A eso vamos.

En Puerto Rico existen al presente tres escuelas de medicina acreditadas por el LCME, las cuales serían las únicas que podrían inmediatamente responsabilizarse ante ACGME de programas postgraduados, fortaleciendo los existentes y desarrollando otros. Alrededor de estas tres escuelas de medicina se desarrollarían las facilidades de tres centros médicos académicos como los define la Asociación de Colegios de Medicina Americanos (AAMC), esto es, compuestos de una escuela de medicina acreditada por el LCME, por lo menos otro programa de otra profesión de la salud reconocido por su respectiva agencia acreditadora, programas reconocidos por ACGME de educación médica postgraduada y un hospital reconocido por la Comisión Conjunta de Acreditación de Organizaciones de Salud (JCAHO).

Ya hace años existe un centro médico académico en la Universidad de Puerto Rico en Río Piedras y otro ha recientemente comenzado en la Universidad Central del Caribe en Bayamón. El tercero, sugiere el autor, debiere lograrse alrededor de la Escuela de Medicina de Ponce y el Hospital Regional de Ponce.

Es la opinión de la mayoría de personas conocedoras de la administración de servicios de salud en Puerto Rico, y consta en el programa de política pública del actual gobierno, que la administración operacional del Departamento de Salud debe descentralizarse, preferiblemente a nivel regional. A tono con dicha política pública creo conveniente que, contractualmente y/o legislativamente,

se le otorgue a dichas escuelas de medicina el control y la autoridad operacional de los hospitales que utilizan como talleres de enseñanza. Claro está, con los presupuestos operacionales razonables y necesarios para su operación. Estas cantidades deberían ser directamente asignadas a dichas instituciones con la debida fiscalización y auditoría operacional de parte del Departamento de Salud. Este Departamento establecería una unidad de inspección general cuyo personal especializado bregaría directamente con dicha auditoría operacional. Además, la operación sería también fiscalizada por el Contralor de Puerto Rico.

Es importante garantizar que las metas de dichas escuelas de medicina deben responder a la realidad del país y responsabilizarse por la prestación de servicios de calidad al paciente al mismo nivel de prioridad que a la docencia. No tengo la menor duda que servicios médicos de calidad y docencia de excelencia pueden ir de la mano.

Estos centros médicos académicos serían la fuente para el país de profesionales de la salud, especialistas en las distintas áreas de la medicina y científicos básicos entre otros. En ellos ocurriría investigación básica y clínica a la medida de nuestros recursos y primordialmente sobre temas afines a problemas de nuestro país. Estos tres centros médicos académicos serían utilizados como instituciones para referidos del sistema de salud público y aun del sector privado de pacientes a nivel terciario y supraterciario.

Se incrementaría en estos centros médicos académicos los programas acreditados por ACGME para adiestramiento postgrado evitando así la fuga de talento a Estados Unidos de muchos de los egresados de nuestras escuelas de medicina acreditadas por el LCME. Debemos recordar que el factor mas influyente en la determinación donde un médico ejerce su práctica es el sitio donde se entrena en su residencia.

La Universidad de Puerto Rico pudiera continuar operando y fortaleciendo los consorcios educativos de Caguas y de Mayagüez con especial énfasis en los programas postgraduados de dichos hospitales.

Es imposible al presente ir mas allá de una vista panorámica de esta propuesta por la limitación impuesta por el medio. Estoy plenamente conciente de la urgencia de elaborar entre los oficiales de las tres escuelas de medicina, el Secretario de Salud y la Legislatura de Puerto Rico un plan detallado para materializar exitosamente esta propuesta.

IV. La Acreditación Local de Programas Médicos Postgraduados

Se refiere el Dr. Ramírez Rivera² a los internados, mal llamados criollos o tainos, con acreditación única del Tribunal Examinador de Médicos. Estos internados no están reconocidos por agencias acreditadoras de Estados Unidos (ACGME) y, por ende, no permiten que estos médicos engranen en el sistema acreditado de educación postgraduada. Este internado, en el mejor de los casos, provee al que "lo sufre" del requisito necesario para obtener la licencia que permite al médico practicar en Puerto Rico al aprobar la reválida. En el peor de los casos provee mano de obra a bajo costo a los hospitales que

utilizan estos médicos tanto en el sector público como en el privado. Lo que resulta ser una realidad, la cual señala muy acertadamente el Dr. Ramírez Rivera,² es "la engañifa de apellidar como internados a estos programas pobremente supervisados en hospitales carentes de estructura educativa formal alguna." (traducción nuestra)

Estos internados deberán ser aprobados por el Tribunal Examinador de Médicos de Puerto Rico. Ese mismo organismo se le responsabiliza por ley de la acreditación de las escuelas extranjeras de medicina. Es obvio que el Tribunal Examinador no cuenta con los recursos ni el expertise necesario para tan importantes funciones. Es evidente que existe en Puerto Rico un doble estandar en nuestra educación médica tanto a nivel subgraduado como postgrado.

A nivel postgraduado existen programas acreditados por ACGME disponibles para graduados de escuelas de medicina acreditadas por el LCME que producirán especialistas que pueden optar por los exámenes de las juntas respectivas de su especialidad. De otra parte, los médicos egresados de escuelas de medicina no acreditadas por el LCME estarían limitados a dichos internados acreditados por el Tribunal y no podrán continuar su adiestramiento completo como especialistas. Esta es lo que he identificado yo como la primera pata de la dupleta del doble estandar de la educación médica en Puerto Rico.

La segunda pata de dicha dupleta del doble estandar de nuestra educación médica es aquella creada en la educación médica subgraduada por el Consejo de Educación Superior. Este organismo tiene al presente la autoridad legal de licenciar (licencia de autorización) y luego acreditar (licencia de renovación) las escuelas de medicina privadas en Puerto Rico aunque las mismas no hayan sido acreditadas por el LCME.

Como resultado de esto existen en Puerto Rico tres escuelas de medicina donde sus estudiantes ostentan las credenciales necesarias para obtener préstamos federales, intercambiar estudios con otras escuelas de medicina de Estados Unidos, recibir entrenamiento en programas postgraduados acreditados por la AMA que le permiten ser elegibles a los exámenes de su especialidad (Board) y pueden optar por solicitar licencia para ejercer la profesión en cualquier jurisdicción de los Estados Unidos en adición a Puerto Rico. Lamentablemente, los egresados de la escuela no acreditada por el LCME no pueden hacer lo mismo. Sería un avance que esta institución pueda lograr en un futuro cercano la acreditación del LCME.

Este doble estandar le impone a Puerto Rico, en los casos en que estos graduados logren su licencia para ejercer la profesión, médicos con un solo año de entrenamiento postgrado y no de la mejor calidad. Está establecido entre los educadores médicos que un estudiante de una escuela acreditada necesita entre tres a cinco años de adiestramiento, bien supervisado después de graduado, para poder ser responsable del manejo de sus pacientes. Como resultado de este doble estandar se empeorará la situación médica del país donde ya 40% de los médicos licenciados en el ejercicio de su profesión no tienen mas de un año de adiestramiento postgraduado y el mismo ha sido en los llamados "internados jíbaros" que son de muy poca calidad y sin la adecuada super-

visión.

El resultado de este internado jíbaro, como muy bien señala el Dr. Ramírez Rivera,² "es la producción de un exceso de médicos mediocres que desalientan la distribución de médicos bien adiestrados en nuestros pueblos". (Traducción nuestra.) También promueven estos internados locales el arresto del desarrollo profesional de estos graduados de escuelas extranjeras al punto que resulta casi imposible cualquier desarrollo adicional.² Señala el Dr. Ramírez Rivera² que estos internados locales o "jíbaros" "solo garantizan la servidumbre de dichos profesionales en Puerto Rico ya que no son reconocidos en ningún otro sitio." (Traducción nuestra.) Y yo añado que la educación médica subgraduada y postgraduada en Puerto Rico que no cuente con el aval de los organismos acreditadores de Estados Unidos debe discontinuarse si es que nos interesa terminar con el doble estandar en la misma y peor aun en el mismo ejercicio de la profesión médica.

El auspiciador que solicitaba el Dr. Ramírez Rivera² "para corregir nuestra mal dirigida trayectoria en educación médica" (traducción nuestra) no puede ser otro que nuestro Gobierno, especialmente nuestra

Asamblea Legislativa y nuestro Departamento de Salud. Los líderes en la educación médica en Puerto Rico debemos aunar nuestros esfuerzos con los del Gobierno para intentar proveer la luz al final del tunel de la educación médica y del ejercicio de la profesión médica en Puerto Rico. De otra forma, estaremos en carrera desenfadada, deteriorando la calidad de los servicios médicos en Puerto Rico. La calidad de la educación médica que determinará la preparación de un médico debe ser gobernada por la excelencia. Recordemos que la norma o estandar jurisprudencial de la práctica de nuestra profesión ya no responde a la norma de la comunidad sino a dicha excelencia en los mejores sitios. Por ende, no hay lugar para el insularismo cuando de la salud de nuestro conciudadanos se trata.

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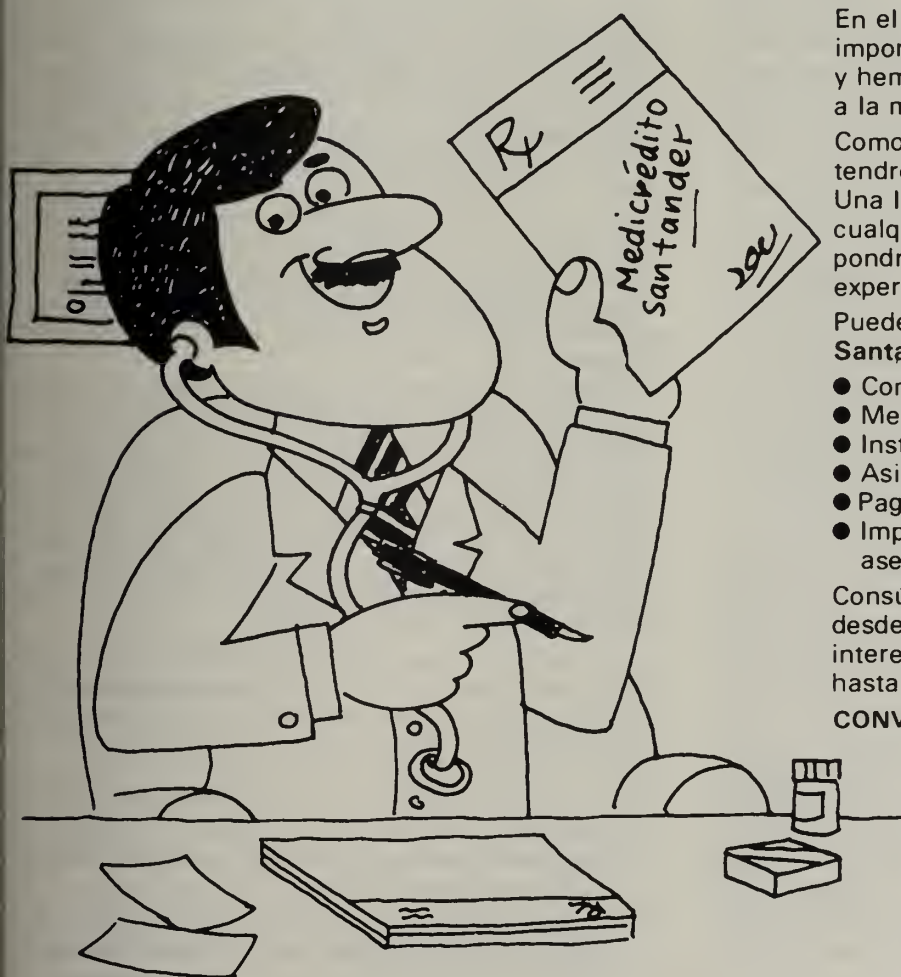
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AMA Policy on the Harvard Resource-Based Relative Value Scale and Related Issues

On December 6, 1988, after almost two days of discussion at its Interim Meeting in Dallas, the American Medical Association (AMA) House of Delegates unanimously adopted Board of Trustees Report AA on the Harvard University resource-based relative value scale (RBRVS) study. Board Report AA states the AMA's position on 18 points related to the RBRVS study and its potential implementation.

The RBRVS is one of a growing list of Medicare physician payment "reforms" considered by Congress and the Administration in the 1980s. Revisions to the current "customary, prevailing, and reasonable" charge system (CPR) that have already been enacted, including payment cuts for procedures deemed by Congress to be "overpriced" and limits on physicians' fees, have made the *status quo* untenable. Proposed alternatives, such as physician DRGs and widespread capitation, pose serious threats to the ability of physicians to continue providing high quality, accessible health care for their Medicare patients.

The Harvard study was initiated in response to a congressional mandate to the secretary of Health and Human Services (HHS) to develop an RVS based on the resource costs of providing physician services and is funded by the Health Care Financing Administration (HCFA). The report of the first phase of the study, which was submitted to HCFA in September 1988, covered 18 specialties. The second phase will extend the RBRVS to an additional 15 specialties. The secretary is required to report back to Congress in July 1989. In its 1988 Report to Congress, the Physician Payment Review Commission (PPRC) stated its support for use of an RBRVS, but not specifically the Harvard RBRVS, to reform Medicare's physician payment system. The PPRC's 1989 Report to Congress, due in March, will contain detailed recommendations on an RBRVS and related issues.

The forthcoming PPRC and HHS reports could lead Congress to enact legislation this year on next directing initial implementation of an RVS-based payment system for 1991 or 1992. The policies adopted by the AMA in Board Report AA clearly state Medicine's position on the critical payment issues. They provide the framework from which the profession can work, over the coming months, to shape the ultimate design of a new system.

The Harvard Study

An RVS is a list of physician services ranked according to "value" in nonmonetary units. In an RVS based on resource costs, relative values are determined by the relative values are determined by the relative costs of the

resources required to provide physician services. Harvard's method of measuring resource costs includes three basic inputs: (1) the physician's work involved before, during, and after providing a service; (2) relative specialty practice cost; and (3) opportunity costs of specialty training. Physicians work is further defined as comprising time, technical skill and physical effort, mental effort and judgement, and stress. The core of Harvard's methodology is a national survey of a randomly-selected sample of practicing physicians in each specialty to determine the relative work entailed in the services provided by physicians in that specialty.

The AMA has been a subcontractor to Harvard since 1986, and is continuing as a subcontractor in the second phase of the original study, which is currently underway. Association efforts are centered around ensuring inclusion of the experiences of practicing physicians in the study by: furnishing advice on the study's methods; working with the national medical specialty societies to secure nominations for the study's physician consultant groups; providing data from the AMA's Socioeconomic Monitoring System; and supplying a nationally representative sample of physicians from the AMA Physician Masterfile.

The final report of the first phase of the Harvard study was released on September 28, 1988. Simultaneous with its submission to HCFA, the study's methods and results were published in the *New England Journal of Medicine*. One month later, the October 28, 1988 issue of the *Journal of the American Medical Association* was devoted exclusively to the Harvard study. Findings from the study and speculation about its implementation also received considerable attention in the media.

Following its release, the AMA distributed copies of the Harvard report to all of the national medical specialty societies and state medical association. Subsequently, the Board of Trustees:

- conducted a technical assessment of the study's methods and results;
- established a special task force to review the RBRVS and related issues; and
- on November 13, convened a meeting of representatives of the state and county associations and national specialty societies to discuss these issues.

Report AA presents the results of the Board's evaluation of the Harvard study and discusses potential use of the Harvard RBRVS in a new Medicare physician payment system. Findings and comments from the Board's assessment, the task force, and the November meeting were reflected in the recommendations contained in Report AA. Also, in response to the testimony of over 100 of the physicians attending the special one-and-a-half-day Reference Committee hearing held prior

to the House of Delegates action on the Board Report, a number of amendments to the Board's original recommendations were adopted by the House.

After considerable discussion, the House voted unanimously to adopt Report AA, as amended, and also called for the Board to Trustees to report back on further RBRVS developments at the June 1989 Annual Meeting, or sooner if necessary. The Reference Committee was careful to point out that the House of Delegates action concerned Board of Trustees Report AA, *not* Harvard's report.

Three Central Policy Statements

The policy agenda outlined in Report AA states three basic positions:

1. Support for an Indemnity Payment System

The first policy statement is a reaffirmation of AMA support for adoption of a fair and equitable Medicare indemnity payment schedule, based on an appropriate RBRVS and monetary conversion factor, under which physicians would determine their fees and Medicare would establish its payments.

2. The Harvard Study

The second position states that the current Harvard RBRVS study and data, when sufficiently expanded, corrected, and refined, would provide an acceptable basis for such a payment system. The Board's assessment of the Harvard study, as well as the testimony of physicians who attended the meetings and hearings on the RBRVS and Report AA, identified a number of areas in the study requiring technical refinement or correction. The RBRVS must also be expanded to additional services and specialties. Much of this work is currently underway at Harvard as part of the second phase of the study.

3. Needed RVS Efforts

The third policy statement calls for the AMA to work with Harvard, the specialty societies, the PPRC, HCFA, Congress, and others to ensure the technical adequacy of the final RBRVS. This recommendation directs particular attention to:

- the restudy of specialties whose RBRVS data have significant, documented technical deficiencies;
- fundamental improvement of the treatment of practice costs;
- revision, refinement, and expansion of pre-and post-service work measurement; and
- expansion and validation of the extrapolation method.

The AMA will also communicate additional concerns that may be identified to Harvard and other appropriate organizations so that these concerns may be properly addressed, and the AMA will work to ensure validation of the results of the results of the additional study.

Together, these three policies form the core of the AMA's position on Medicare physicians payment reform. The Association will seek to move Medicare away from the complex and arbitrary regulations that have characterized the current payment system toward an approach based on the resource costs of providing physician services. The current Harvard RBRVS is the starting point for developing such a system, and the AMA will work with others involved in payment reform to ensure completion of an acceptable final RBRVS for use in a new Medicare payment schedule.

In addition to policy on an acceptable basis for the schedule of payments, a new payment will require policy on other important design features. The AMA positions on key implementation issues are stated in Board Report AA and are summarized briefly below.

Balance Billing

Retention of the ability to bill patients for the difference between the amount that Medicare pays and the physician's actual charge for services provided to Medicare patients ("balance billing") remains a cornerstone of AMA policy. Report AA:

- reaffirms the AMA's opposition to elimination of balance billing and opposition to continuation of Medicare maximum allowable actual charge (MAAC) limits;
- calls for enhanced physician discussion of fees with patients as an explicit objective of a Medicare indemnity payment system; and
- recommends expanded support for state and county medical society-initiated voluntary assignment programs for low-income beneficiaries.

Report AA clearly distinguished between an RBRVS-based indemnity payment system and a fixed fee schedule. The Harvard RBRVS is based on the average relative resource costs required to deliver a service to the average patient. Balance billing must be preserved in order to recognize differences between physicians in quality, experience and practice costs, as well as differences between patients in severity of illness and access to care. It is the position of the AMA that it is impossible to develop a fixed fee schedule that could either account for all of these factors with the necessary precision or assure Medicare patients continued access to their physicians of choice.

Transition

A transition period reduces the change in the payment system in any given year. The AMA supports phasing in any new payment system in order to minimize disruption in the delivery of physician services. Report AA recommends that the new Medicare payment system be implemented using a progressive blend of RVS-based payments and CPR payments. It also recommends that the specific length of the transition period be chosen in order to appropriately minimize both disruption for patients and the complexity of the process.

Geographic Payment Variations

The RBRVS, of course, measures national average resource costs; geographic payment variations would arise from the use of geographic multipliers to the monetary conversion factor. Report AA reaffirms the AMA's current policy that such payment variations should reflect valid and demonstrable geographic differences in practice costs, particularly the cost of professional liability insurance. Based on data availability, payment localities in the new system could consist of a combination of regions, states, and localities states. The report also recommends that payments be adjusted where necessary to remedy access problems in specific geographic areas, and that geographic differentials and specialty differentials be addressed simultaneously.

Specialty Differentials

A specialty differential is a difference in the amount paid to different specialists for services designated by the same procedure code. Whereas specialty differentials in the current system are based on differences in charging patterns among specialties, differentials in an RBRVS-based payment system could arise from differences among specialties in either the level of work, practice costs, or training costs required to deliver a service. The current Harvard data do not yet provide a solid basis for determining whether and for what services such differentials might apply.

The AMA adopted the general principle that for services that meet two criteria, an RBRVS-based payment schedule should include specialty differentials: when resource costs for a particular CPT-coded service are substantially different across specialties, and when the procedure codes are not sufficiently precise to differentiate the physician work of a service across specialties. For services that meet these criteria, the AMA's position is that the differential payment should apply both when the services that specialists provide are within their specialty and when these same services are provided as general or primary care. AMA policy further states that, where differentials exist, designation of specialists should avoid dependence on rigid criteria, such as board certification. Instead, general national guidelines should be established, with carriers having sufficient flexibility to respond to local conditions.

Other Implementation Issues

In two policy statements, Report AA affirms the AMA's strong opposition to use of any new Medicare payment system to introduce cuts, freezes, or enforced targets for Medicare expenditures for physician services aimed at producing federal budget savings. The Association believes that expenditure targets will lead to rationing of care for Medicare patients, and instead supports constructive approaches to enhancing quality and appropriateness of care.

In updating the RBRVS and conversion factor, the House adopted the position that only one organization, the American Medical Association, has the resources, experience, and umbrella structure necessary to represent the collective interests of Medicine. This recommenda-

tion calls for the AMA to seek such a role in whatever update process is selected, and to do so in a manner that enables full participation from all of organized medicine, especially the national medical specialty societies.

Conclusion

Report AA will not be the final AMA report on the RBRVS and its implementation. In adopting Report AA, the AMA has adopted positions on a number of the key policy issues in the development of a new Medicare physician payment system. Adoption of this report will enable the American Medical Association and its leadership to continue to play a central role in policy debates on Medicare physician payment. At the same time, the report explicitly states that much work is needed before a final Medicare RBRVS can be implemented. The AMA will continue to expend all necessary efforts to ensure both the completion of a technically adequate RBRVS and its appropriate use by the PPRC, Congress, and HCFA in a Medicare indemnity system.

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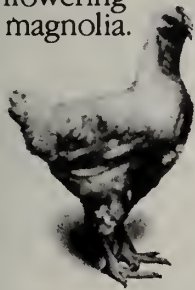
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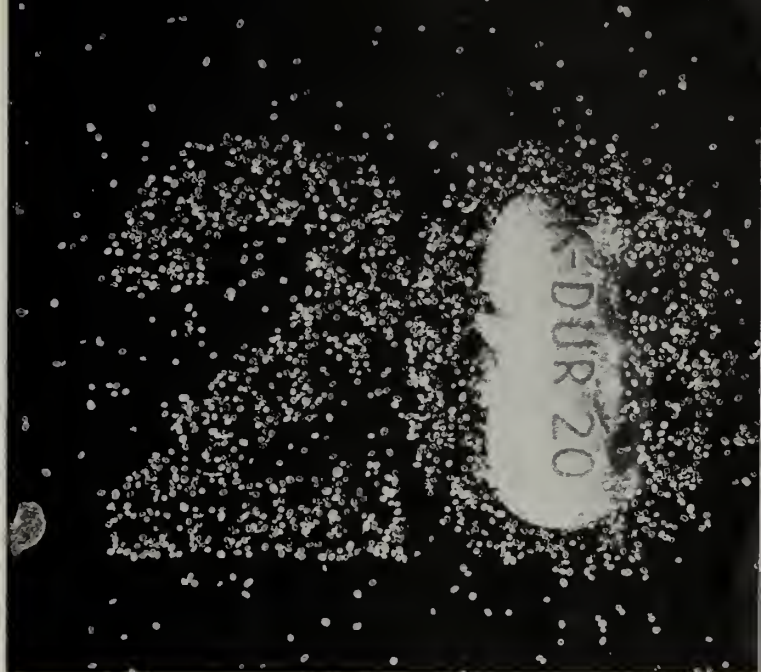
1. I think I have lumbago.
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3. I'm on the grapefruit diet.
4. I gave six months ago.
5. I just got back from Monaco.
6. The lines are thirteen blocks long.
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1 For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2 For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3 The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-OUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-OUR tablets is, at present, unknown. K-OUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-OUR. It is also not known whether K-OUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-OUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, AND OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS AND WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS AND WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

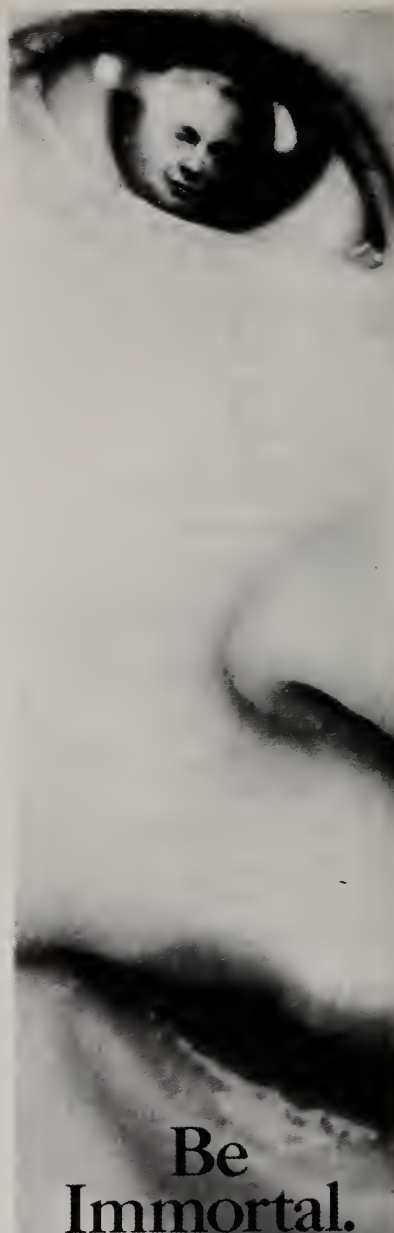
- 1 Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
- 2 Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
- 3 Correction of acidosis, if present, with intravenous sodium bicarbonate.
- 4 Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Mirada a Nuestro Pasado - Hace 50 Años...

Tonsilectomía: Sus Indicaciones*

C.E. Muñoz Mac Cormick, MD

Es mi intención presentar de un modo informal, breve y sencillo, el consenso de opinión dentro de la clínica moderna en lo que respecta a la tonsilectomía sin limitarme, al así hacerlo, a consideraciones puramente laringológicas, sino tomando también en consideración lo que la medicina interna y la pediatría nos aconsejan en este respecto.

La disparidad de criterio prevaleciente en cuanto a los beneficios a derivarse de la tonsilectomía en condiciones que hasta hace poco creímos casi específicamente atribuibles a amígdalas enfermas; la avalancha de intervenciones de esta índole que en manos poco escrupulosas, y muy en contra del sentir y pensar de pediatras y clínicos prominentes y de laringólogos concienzudos ha llegado a crear la convicción de que el que posee aún sus amígdalas no está a la moda; la experiencia por que casi todos los médicos generales han pasado de ver sus esperanzas frustradas al notar un empeoramiento sintomatológico después de la tonsilectomía en pacientes suyos a quienes se les había prometido una curación completa si se extirpaban las amígdalas, fracaso atribuible en ciertos casos a una ablación incompleta y en otros a la ablación de amígdalas inocentes; todo esto ha creado cierto grado de incertidumbre y desasosiego en la mente del médico general que le resta a su fe y no le permite dictar, con la seguridad y firmeza con que quisiera él hacerlo, un fallo bien sea condenatorio o absolutorio al presentárselo para su decisión un posible candidato a la tonsilectomía.

Las amígdalas, aunque sus funciones fisiológicas no están aún completamente esclarecidas, entran en la formación del anillo de Waldeyer, y por lo tanto forman parte integrante de la primera línea de defensa contra invasiones patógenas a través de las regiones faríngea y naso-faríngea. La segunda línea de defensa queda constituida por los ganglios linfáticos, según los experimentos de V. Lenart, quien observó que sustancias inyectadas en la nariz eran parcialmente interceptadas por las amígdalas, otra parte siendo recuperada en los ganglios cervicales. Oppel y Cinelli dan énfasis a las propiedades citogénicas de las masas linfoides que entran en la formación de las amígdalas. Histológicamente se ha corroborado que los centros germinativos producen linfocitos, los cuales emigran constantemente a través del epitelio,

fagocitan las bacterias en las criptas y son luego destruidos en los ganglios linfáticos. Pero recordemos que esta protección, este proceso inmunológico, constituye el funcionamiento de una amígdala normal. Hay que recalcar el hecho de que esta protección amigdalina es más acentuada en niños menores de seis años y explica de esta manera la aumentada susceptibilidad a infecciones del trayecto respiratorio superior en niños menores de cinco años a quienes se le han extirpado las amígdalas estando éstas normales.

Recordemos que las criptas amigdalinas son largas y bifurcadas y que un gran número de ellas demuestran una marcada estrechez en su extremo faríngeo; de ahí que ofrecen tan adecuado albergue a los invasores bacterianos. Se inicia la infección, sigue una hiperplasia de las criptas con su acumulación concomitante de debris epitelial y células inflamatorias; se ocluye el ya estrecho extremo faríngeo de la cripta y tenemos una excelente incubadora para las bacterias allí presentes. Entorpecido así el drenaje no solamente quedan las bacterias multiplicándose en las criptas, ahora más bien saquitos cerrados, e invadiendo otras líneas de defensa sino que sus productos y toxinas solubles son lanzadas con facilidad al torrente sanguíneo. Se intensifica la batalla ahora en la segunda línea de defensa, se infartan los ganglios linfáticos regionales en su lucha por compensar no solamente la deficiencia protectora de la amígdala enferma sino lo que es mucho más, la traición de su primera línea de defensa que ahora la alberga el enemigo y lo coloca en posición ventajosísima para invadir y atacar inmediatamente que por cualquier razón bajase la resistencia bien local o general del organismo. Esa es una amígdala patológica y su ablación como tratamiento electivo está absolutamente indicada.

¿Pero, desde el punto de vista clínico, cuando debemos aconsejar la tonsilectomía? Al presente podríamos enumerar las indicaciones del siguiente modo:

1. Ataques recurrentes de amigdalitis y periamigdalitis.
2. Obstrucción respiratoria.
3. Amigdalitis lacunar crónica cuando es el foco de infección, produciendo manifestaciones sistemáticas.
4. Dolores articulares recurrentes como consecuencia de ataques agudos o subagudos de amigdalitis.
5. Prueba de que las amígdalas son portadoras de la difteria.
6. Recrecimiento crónico de los ganglios cervicales situados detrás del ángulo de la quijada.

*Boletín de la Asociación Médica de Puerto Rico, Vol. 31, pp 323-329, 1939

Otros autores, enumeran sus indicaciones como sigue:

1. Ataques recurrentes de amigdalitis aguda o de abscesos periamigdalícos.
2. Catarro nasal constante.
3. Respiración nasal obstruida.
4. Adenitis cervical, si comprobada ser de origen amigdalino.
5. Hipertrofia amigdalina cuando ésta es suficientemente marcada para interferir con la respiración o deglución normal.
6. Historia clínica que revele ataques de otitis media catarral o supurada.
7. Respiración por boca.
8. Ataques recurrentes de faringitis; laringitis o bronquitis.
9. Historia de reumatismo, endocarditis, corea o nefritis.
10. Amígdalas portadoras de difteria.
11. Infección tuberculosa de las amígdalas — con sumo cuidado en la selección de casos.
12. Secreción nasal constante en la ausencia de sinusitis.
13. Amígdalas "sepultadas" decididamente patológicas.

Cinelli de una manera muy hábil expone las indicaciones para la tonsilectomía bajo una clarificación de las varias condiciones en las cuales la operación generalmente se practica. Seguiremos esa clasificación, con algunas modificaciones, en la presentación y discusión de este trabajo.

Hipertrofia amigdalina (incluyendo la tonsilitis lacunar crónica.)

Hipertrofia excesiva obstaculizando la respiración y deglución normal.

Aunque las amígdalas generalmente tienden a atrofiarse en la pubertad, las hipertrofias amigdalinas se observan en todas las edades. La tendencia hereditaria a la hipertrofia de los tejidos linfáticos se observa marcadamente en muchas familias. La consistencia puede ser linfoidea o fibrótica, la primera más frecuentemente observada en los niños, la segunda en los adultos. Stoker cree que la incidencia de hipertrofia amigdalina es más frecuente en niños malnutridos y añade que aún después de la operación no hay gran mejoría en estos casos si no se suministra una dieta rica y bien balanceada.

La irritación constante producida por la secreción retenida en las criptas, por la respiración por boca en casos de obstrucción nasal, y por ataques recurrentes de amigdalitis tienden a producir hipertrofia de las amígdalas, de ahí que Birkett recomienda en niños de varios meses a cuatro años de edad, en los cuales se observa solamente una hipertrofia moderada de las amígdalas con obstrucción nasal marcada de origen adenoideo, que se practique la adenoidotomía, asegurando que si se restablece la respiración nasal normalmente, las amígdalas recederán prácticamente a su tamaño normal. Hago hincapié en que se trata de amígdalas que se notan sanas a no ser por su tamaño exagerado.

Quiero llamar la atención en cuanto al reconocimiento de las amígdalas en la leucemia linfática y a la posibilidad de confundir una condición maligna de las amígdalas con una simple hipertrofia. En el sarcoma, si observamos

cuidadosamente, notaremos que la amígdala es de una consistencia dura y que la membrana mucosa que la cubre exhibe numerosos vasos sanguíneos de pequeño calibre.

Infección crónica

La amígdala hipertrófica con su inflamación aguda, pilares rojizos, e historia típica de anginas frecuentes no ofrece gran dificultad al diagnóstico. Es la amígdala pequeña, "sepultada", aparentemente normal, sin historia de anginas frecuentes, la que presenta mayores dificultades al clínico. Una historia cuidadosa del caso es esencial. Casi siempre admitirán haber sufrido un fuerte catarro nasal precedido de intenso dolor de garganta; o nos revelarán algún trastorno en la región amigdalina. Al examen objetivo debemos tratar de esprimir pus de las criptas y en casos positivos obtendremos, especialmente del polo superior, además de los "tacos" típicos, una sustancia purulenta, rala, cuya consistencia se semeja a la de la leche; examinar cuidadosamente las glándulas cervicales, muy especialmente las del ángulo de la quijada; observar el color de los pilares, especialmente el anterior, pues un enrojecimiento de la mucosa en esta región, dando el aspecto de una inflamación aguda, es indicativo de una infección en las amígdalas. Esta clase de caso difícil es el que con más frecuencia actúa como foco de infección en condiciones sistémicas y más adelante hacemos referencia nuevamente a él.

Infecciones del trayecto respiratorio superior

Aquí podemos incluir:

- Tonsilitis recurrente
- Catarros nasales persistentes
- Otitis media
- Sinusitis

En esta clase de casos siempre que se comprobase la infección en las amígdalas, resulta ser sumamente beneficiosa la tonsilectomía y adenoidotomía. Un estudio cuidadoso de casos pertenecientes a este grupo que no mejoran con la tonsilectomía demostró que la persistencia de la sintomatología era atribuible a una a varias de las siguientes razones:

1. Ablación incompleta, habiéndose dejado fragmentos de tejido tonsilar infectado, muy especialmente tejido inferior tonsilar.
2. Enucleación incompleta de los adenoides.
3. Hiperplasia marcada del tejido linfoideo de la faringe compensatorio a la adenoidotonsilectomía, siendo este tejido responsable de la reaparición del mismo tren sintomatológico existente antes de la intervención.
4. Operadores ultra-radicales llevándose con el adenoidotomo la pared posterior de la trompa de Eustaquio en la región del "Torus turbae" produciendo una estenosis cicatricial con empeoramiento de la otitis y pérdida de audición que habían motivado la tonsilectomía.
5. Aunque generalmente una sinusitis maxilar reciente cura de por sí después de la tonsilectomía, hay casos

en que la infección es ya muy avanzada y continúa a pesar de la ablación amigdalina, requiriendo el seno de por sí un tratamiento adecuado. Si esta sinusitis, ha pasado inadvertida, la sintomatología que creíamos desaparecería con la tonsilectomía lógicamente ha de continuar mientras no se le preste la debida atención al seno enfermo.

6. Con la moda de tonsilectomía al por mayor no se le presta debida atención a los casos individualmente, y esto da origen a que muchos niños pierden de este modo sus amígdalas, amígdalas completamente normales que no han cometido otro desafuero que el de aparecer un poco más crecidas de lo corriente.

A estos niños se les ha robado una línea de defensa y quedarán, lógicamente, más susceptibles a catarrros e infecciones del trayecto respiratorio superior que antes de la operación. Es verdad que un niño sin amígdalas está mucho más saludable y resistente, especialmente en cuanto a catarrros concierne, que un niño con amígdalas enfermas, pero nunca más que un niño con sus amígdalas sanas.

Bronquitis crónica, laringitis, y alergia

Las amígdalas enfermas han sido consideradas por algunos autores como factores etiológicos en estas condiciones. Kaiser informa que la tonsilectomía no cura estas bronquitis, es más, es posible que las empeore. Cinelli cita varios casos en que las amígdalas linguales, habiéndose hipertrofiado en reacción compensatoria a la tonsilectomía, causaron el empeoramiento de la bronquitis, la cual mejoró notablemente al ser aquellas electrocoaguladas. En otros casos halló como causa del empeoramiento post-operatorio una hiperplasia de los folículos linfoides faríngeos, mejorando la bronquitis en cuanto estos fueron debidamente tratados. En la laringitis, con muy pocas excepciones, no podemos asegurar resultados satisfactorios con la tonsilectomía.

En cuanto a las manifestaciones alérgicas en los niños ha quedado comprobado por varios autores que la adenoidotonsilectomía no aportará resultados satisfactorios más que aliviar los catarrros frecuentes.

La alergia nasal o pulmonar tienen la misma incidencia en casos con amígdalas que en casos sin amígdalas. Algunos autores opinan que la ablación de las amígdalas y adenoides en un individuo alérgico frecuentemente ha precipitado el desarrollo de alergia nasal, asma, o ambas.

No es mi intención impresionarles con la idea de que en un caso de alergia no se deben extirpar las amígdalas si éstas están enfermas. No, al contrario, queda indicada la ablación al igual que en cualquier otro caso de un niño normal cuyas amígdalas estuviesen en iguales condiciones, pero es necesario tomar más precauciones en estos casos, intensificar el tratamiento alérgico y preparar aún mejor al paciente para evitar complicaciones indeseables.

Queda, pues, indicada la tonsilectomía en esta clase de casos única y exclusivamente cuando las amígdalas demostrasen infección activa y el estado de ellas de por sí lo requiriese, pero nunca como parte de un tratamiento rutinario en estas condiciones.

Condiciones sistémicas

Fiebre reumática

Cineli recomienda la tonsilectomía en la etapa prodromal del síndrome reumático; dolores musculares, teno-sinovitis, miositis, y neuritis, acompañados de dolor de garganta. Opina, sin embargo, que una vez que se ha iniciado la fiebre reumática aguda, o la artritis aguda, el pronóstico de la tonsilectomía debe ser muy reservado. Si ya se han manifestado cambios destructivos en las articulaciones, los resultados son pobres.

Ash ha dado a la publicidad un excelente trabajo sobre la influencia de la tonsilectomía en las infecciones reumáticas. Considera la posibilidad de que la tonsilitis, cuando ésta acompaña a la fiebre reumática aguda, sea no más que una manifestación de una infección generalizada y no el portal por donde entra la infección inicial tornándose luego en foco de infección crónico. Analiza el efecto de la tonsilectomía sobre el curso de la enfermedad en 522 niños reumáticos e informa que con la operación no logró evitar nuevas manifestaciones reumáticas en su serie. El hecho de que las amígdalas hubiesen sido o no extirpadas antes del comienzo de la enfermedad o que fuesen extirpadas después de manifestados los síntomas reumáticos no parece haber influenciado de un modo notable la incidencia de complicaciones cardíacas ni la mortalidad. Una incidencia alta de exacerbaciones reumáticas fueron observadas como complicación de la intervención llevada a cabo temprano en el curso de la enfermedad. La ablación, si está indicada, debe ser completa y hecha por manos expertas.

En conclusión, la tonsilectomía en el niño reumático está indicada únicamente cuando las amígdalas están infectadas y ellas de por sí lo requieren, y nunca como un tratamiento de rutina. La operación, en los casos en que está indicada, deberá practicarse durante una fase inactiva de la enfermedad, entendiéndose por fase de inactividad cuando, en ausencia de síntomas, se consiga un período afebril acompañado de una cifra de sedimentación eritrocítica normal.

Enfermedades cardiovasculares

Muchos autores aseguran haber obtenido buenos resultados de la tonsilectomía en casos incipientes, especialmente de origen reumático, siempre que la intervención fuere practicada en el comienzo de los síntomas y signos cardíacos, cuando éstos aún sean de un carácter muy leve o transitorio. Una vez se hayan registrado cambios destructivos en el miocardio o endocardio, el beneficio de la tonsilectomía, si lo hay, será muy poco.

Mi impresión es que siempre que haya una infección marcada de las amígdalas, aún en casos relativamente avanzados del corazón, la tonsilectomía puede aportar una notable mejoría en el estado general del paciente y contribuir a la compensación cardíaca. Antes de intervenir, sin embargo, el paciente debe ser objeto de un cuidado esmerado, su resistencia y estado general traídos a un nivel de seguridad razonable y esperar, como ya hemos apuntado, una fase de inactividad para intervenir.

Trastornos génito-uritarios

Varias condiciones agudas del trayecto génito-urinario guardan estrecha relación con la amigdalitis. En casos de nefritis hemorrágica aguda, pielitis y albuminuria persistente, cuya causa no puede determinarse con exactitud, un examen detenido de las amígdalas las inculpará como responsables de dichos trastornos, y la tonsilectomía aportará en la mayor parte de los casos una rápida curación.

Afecciones de la tiroides

De acuerdo con las observaciones de Cinelli, la tiroides y las amígdalas, en ciertos casos tratados por él, han demostrado estar relacionadas. El alude a un caso de tiroiditis aguda como complicación de una tonsilectomía, y a dos casos de bocio adolescente que curaron después de extirparse las amígdalas.

En la tirotoxicosis la tonsilectomía está indicada y según él debe practicarse. Si la tirotoxicosis es muy avanzada, debe tratarse primero la tiroides y luego extirparse las amígdalas. Cuenta él de varias exacerbaciones agudas de la tiroides después de haber sido tratada ésta quirúrgicamente, que fueron causadas por amígdalas crónicas, y que curaron por completo después de la tonsilectomía.

Enfermedades infecciosas

Nos limitaremos aquí a recordar que las amígdalas portadoras de difteria deben ser extirpadas. Y en justo favor a la tonsilectomía, ya que estamos hablando de difteria, deseo apuntar que la mortalidad y las complicaciones en niños sin amígdalas que contraen la difteria son mucho más bajas que en niños que aún las poseen. Bailey reporta 6,000 casos de difteria y alega no haber tenido una sola defunción en casos en que las amígdalas y adenoides habían sido previamente extirpadas.

Resumen: La tonsilectomía, juiciosa e inteligentemente aconsejada, y en manos expertas, trae consigo resultados excelentes, a veces espectaculares, en infecciones del trayecto respiratorio superior, y ciertas condiciones sistémicas.

La tonsilectomía "en masa" como tratamiento rutinario de condiciones sistémicas es censurable.

La cooperación mas decidida entre el clínico y el laringólogo es indispensable en el tratamiento científico de condiciones sistémicas posiblemente atribuibles a infección focal, tales como la fiebre reumática y sus complicaciones cardíacas. La tonsilectomía, en casos de esta índole, si es producto de esta estrecha cooperación tendrá todas las probabilidades de éxito, mas, si por el contrario, se practica caprichosamente en el momento impropio y en condiciones adversas habrá de fracasar y posiblemente traer resultados funestos.

COMENTARIO

Indicaciones de Tonsilectomía 1939 y 1989

Antonio Rullán, MD, FACS*

El artículo por el doctor C.E. Muñoz-Mac Cormick publicado en el Boletín de la Asociación Médica de Puerto Rico hace 50 años fue y es magnífico. La redacción y organización del texto es excelente. El uso del castellano impecable y las referencias utilizadas fueron muy buenas.

Las indicaciones para el procedimiento siguen siendo las mismas que señaló el doctor Muñoz-Mac Cormick, como también lo sigue siendo el sobreuso de la operación. Hoy en día con el uso de antibióticos se han reducido ambas.

Referente a si la operación puede precipitar el desarrollo de asma es asunto aún controversial. No hay duda que cuando se extirpan unas amígdalas en casos de asma infecciosa se le quita el asma. Esto lo he podido comprobar por experiencia propia en las miles de amígdalas que he extirpado, la mayor parte de ellas en hospitales del gobierno.

El primer párrafo del Resumen del artículo del doctor Muñoz-Mac Cormick sigue teniendo la misma vigencia en 1989 que 50 años atrás con relación a las indicaciones de la amigdalectomía: "La tonsilectomía, juiciosa e inteligentemente ejecutada en manos expertas trae consigo resultados excelentes, a veces espectaculares, en infecciones del tracto respiratorio y ciertas condiciones sistémicas."

*Profesor de Otorrinolaringología (Retirado), Escuela de Medicina, Universidad de Puerto Rico

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MEDICAL ASPECTS OF NUTRITION

Salt Intake and Blood Pressure in Humans*

Myron H. Weinberger, MD**

The sodium ion has long been known to exert an adverse effect on blood pressure. Epidemiologic data demonstrates an association between dietary sodium intake, the presence of hypertension and the cardiovascular consequences thereof. Dietary sodium restriction and its therapeutic analogue, diuretic administration, have been the mainstay of antihypertensive therapy. Recent studies, however, have forced reevaluation and critical scrutiny of the role of sodium in human blood pressure control because of two observations. The first is that not all individuals respond to an excess of sodium with a rise in blood pressure. Second, not all individuals show a decrease in blood pressure in response to reduction in sodium and extra-cellular fluid volume by dietary sodium restriction or diuretic administration. Furthermore, elucidation of interactions between sodium and other dietary constituents, such as potassium and calcium, has further confounded this relationship. New observations, suggesting that sodium sensitivity or resistance of blood pressure may be the result of genetically mediated or acquired abnormalities, have kindled further interest in this area.

History and Epidemiology

The notion that sodium intake could be deleterious to health was first recorded in the *Yellow Emperor's Classic of Medicine* 4,500 years ago. Recent reviews have surveyed the apparent relationship between dietary sodium consumption and prevalence of elevated blood pressure as well as the consequences of hypertension.¹ Generally, in societies where habitual dietary sodium intake exceeds 50-100 mEq per day, hypertension is a common finding and increases with increasing levels of sodium intake. However, societies ingesting lower levels of sodium in whom hypertension and its cardiovascular

consequences are rare are also frequently genetically homogeneous, isolated, primitive and have high physical activity. Furthermore, diets low in sodium are often high in potassium and calcium. Among acculturated societies in whom sodium intake is high, a rise in blood pressure with increasing age is typical.¹ In contrast, the rise in blood pressure with age, typically observed in industrialized nations, is not generally seen among those societies where sodium consumption is below these levels.

Interventional Studies

The Samburu tribesmen of Kenya normally ingest in excess of 200 mEq of potassium per day and a very low sodium level. When recruited into the Kenyan army, these individuals demonstrated a significant rise in blood pressure with adoption of salty army rations. When they resumed their native diet after completion of their military service, blood pressure again declined.¹ Similar observations have been reported in natives typically ingesting a low sodium intake when living in primitive areas in the South Pacific, who adopted the higher sodium intake of their compatriots after leaving their native territory.¹

At the Indiana University School of Medicine, a study was conducted among normotensive young men. Observations of blood pressure, as well as a variety of physiological factors, were made. Following equilibration on a low (10 mEq/day) sodium intake, subjects were subjected to 3-day periods of sodium balance at incremental levels of sodium intake of 300, 600 or 800, and 1200 or 1500 mEq of sodium per day.² These studies demonstrated a significant increase in blood pressure with this marked dietary sodium loading. Furthermore, the racial composition of the participants in the study permitted us to identify increased sensitivity of the blood pressure-raising effects of sodium in black subjects compared to whites. In that study, sodium loading above the 300 mEq/d level resulted in net potassium deficit. When these potassium losses were prevented in a subsequent study by administration of potassium supplementation on a daily basis to replace losses, the blood

*Contemporary Nutrition, Vol. 13, No. 8, 1988. Reprint with permission from General Mills, Inc. Minneapolis, Minnesota.

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pressure rise associated with sodium loading was significantly attenuated, providing confirmation of the modulatory effects of potassium balance on the expression of sodium's effect on blood pressure. The impact of modest dietary sodium restriction in societies which typically consume large amounts of sodium is also worthy of mention.

The Japanese are known to have a sodium intake as high as 25g of sodium chloride per day or more. Hypertension is very common in Japan and stroke is one of the most frequent causes of death, a direct consequences of elevated blood pressure. A public health campaign, which reduced dietary sodium intake by about 15% between 1971 and 1981, was associated with a significant reduction in the prevalence of hypertension and stroke.¹ Even in newborns, sodium can be shown to exert an effect on blood pressure. Dutch physicians randomly assigned infant formula with a normal or low sodium content to a group of newborns.³ At the end of 6 months, those given the lower sodium formula had significantly lower blood pressure.

A blood pressure-lowering effect of severe dietary sodium restriction (<10 mEq/d) has been recognized for over 65 years. Before the advent of diuretic therapy (1958), the "Rice Diet" of Kempner, which was high in potassium as well as low in protein and sodium, proved life-saving for many severe hypertensive subjects. However, not all hypertensives achieved blood pressure reduction with these severe dietary modifications and most found them unpalatable for extended periods of time. Current evidence suggests that the magnitude of blood pressure response to reduction of dietary sodium intake is dependent on the initial level of blood pressure and is highly variable.¹ Modest dietary sodium restriction (70-80 mEq/d) is effective in reducing blood pressure in many hypertensive subjects. Furthermore, the use of such modest and achievable levels of dietary sodium restriction, in combination with antihypertensive therapy, has permitted blood pressure control in subjects in whom control was difficult previously or permitted maintenance of blood pressure control with less medication, enhancing compliance, reducing side effects and expense.

Heterogeneity of Blood Pressure Response

It has long been recognized that the risk for development of hypertension is variable on the basis of factors other than dietary sodium intake and include racial or ethnic background and genetic endowment as well as acquired alterations in kidney functions which govern the ability to handle a sodium load. Many studies have demonstrated that not all normotensives or hypertensives respond to increases or decreases in dietary sodium in the same fashion. Some individuals decrease blood pressure with dietary sodium restriction or diuretic administration while others increase blood pressure in response to the same maneuver.

Studies were conducted at the Indiana University Medical Center in normotensive and hypertensive subjects using two different approaches to evaluate blood responsiveness to sodium and extracellular fluid volume balance.⁵ The first of these studies utilized a protocol

designed to 'rapidly expand body sodium and fluid content and to rapidly contract it. This was accomplished by the intravenous administration of normal saline (2 liters over a 4-hour period) followed on the next day by sodium and volume depletion achieved by a low sodium intake (10 mEq/d) and three doses of a potent loop diuretic, furosemide, 40 mg each. The second study was conducted in normotensive subjects using a 3-month period of modest (<75 mEq/d) dietary sodium restriction and a further study in treated hypertensive subjects over a 6-month period of similar reduction in dietary sodium intake.

In response to the rapid sodium and volume expansion and contraction protocol, marked heterogeneity in blood pressure responsiveness was observed in normotensive as well as hypertensive subjects. Decreases in mean arterial blood pressure exceeding 15 mmHg following sodium and volume depletion were seen in both populations. Increases in blood pressure of similar magnitude were also seen in both normal and hypertensive subjects in response to a low sodium diet and diuretic administration. Utilizing arbitrary definitions of sodium sensitivity and resistance based on these blood pressure changes, it was observed that over 50% of the hypertensive population were sodium sensitive and one-third were sodium resistant.⁵ In the normotensive population, only 26% were found to be sodium sensitive while half were sodium resistant. Similar heterogeneity of blood pressure response to dietary sodium intervention was observed in the normotensive population. Decreases as well as increases in mean arterial pressure exceeding 10 mmHg were observed in these normal adults. In the hypertensive subjects participating in the dietary sodium restriction study, significant decrease in mean arterial pressure was observed in those who were compliant with reduced sodium intake in comparison to those who were not able to achieve the therapeutic goal and maintain it for six months or longer.⁴ An additional benefit of compliance with dietary sodium restriction was that many patients reduced the amount of medication required to maintain their blood pressure control.

In examining responsivity to sodium from these studies, several interesting observations emerged. Sodium-sensitive subjects tended to be older than those who were sodium resistant, suggesting a role for sodium in the age-related increase in blood pressure.⁵ Furthermore, sodium-sensitive subjects tended to have lower levels of plasma renin activity and to respond to sodium and volume depletion with less increase in plasma renin activity than their sodium-resistant counterparts. A blood protein, haptoglobin, was more likely to be of the 1-1 phenotype among sodium-sensitive individuals than resistant subjects, while individuals having the 2-1 or 2-2 phenotype were more apt to be sodium resistant.⁶ These observations suggest a genetic basis for sodium sensitivity and resistance. Such a genetic factor could explain why not all individuals who are exposed to a high dietary level of sodium develop hypertension. Perhaps at risk are those whose genetic endowment or acquired decrease in renal function has made them sensitive to the blood pressure-raising effects of sodium.

Potassium supplementation appears to have inconsis-

tent or negative effects on blood pressure of normotensive individuals ingesting a normal dietary intake of potassium.⁷ However, in diuretic treated, potassium-depleted hypertensive subjects, potassium supplementation appeared to have a beneficial effect in reducing blood pressure.⁸ Calcium supplementation has also been demonstrated to have a heterogenous effect on blood pressure in normal and hypertensive subjects.^{9, 10} The magnitude of blood pressure response to calcium supplementation at present seems to be less than that of the majority of studies with sodium and to exert an effect on a smaller number of individuals. However, in comparison to the voluminous data regarding sodium in normal and hypertensive humans, the present evidence concerning potassium and calcium are quite scanty and require further confirmation and study. A recent study has demonstrated that only when sodium is given in the form of chloride salt does it raise blood pressure in sodium-sensitive hypertensives.¹¹ The clinical relevance of this observation, however, many be blunted by recognition of the fact that most of the sodium consumed in dietary sources is in the form of the chloride salt.

Summary

Abundant evidence exists to link the dietary intake of sodium to the development of high blood pressure and the potential occurrence of cardiovascular consequences including stroke, congestive heart failure and other forms of cardiovascular disease as well as renal failure. Not all individuals are sensitive to the blood pressure-raising effects of sodium. Genetic or acquired factors may determine an individual's ability to handle the sodium load. In sodium-sensitive hypertensives, modest dietary sodium restriction is beneficial in both reducing blood pressure and in controlling the elevated pressure with medication. A role for potassium and/or calcium with respect to the effects of sodium is an intriguing area of current inquiry.

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BRIEF SUMMARY

CARDIZEM[®] SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

- Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment,

may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1% have been observed in angina trials. In many cases, the relation to drug uncertain).

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, ST and LOH (see hepatic warnings), vomiting, weight increase, thirst.

Dermatological: Patches, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nodules, osteoarthritis, pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1

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SMOKING HAS HARMFUL EFFECT ON HOW BODY FAT IS DISTRIBUTED: STUDY

Although it might help people lose a few pounds, smoking cigarettes paradoxically leads to a redistribution of body fat that is associated with increased risk of heart disease, diabetes, and early mortality, says a study in the *Journal of the American Medical Association*.

"Cigarette smokers, as a group, weigh less for their height than nonsmokers, and cessation of smoking leads to significant weight gain," say the authors, Hiroshi Shimokata, MD, and colleagues at the National Institute on Aging, Baltimore. In their study of 1,122 men, the authors report that weight and body mass indexes were significantly lower in cigarette smokers than in nonsmokers, when age was taken into account. However, when they examined the ratio between waist circumference and hip circumference, they found smokers had significantly larger waist-hip ratios (WHR) than nonsmokers. There was also a graded dose-response relationship between this ratio and the number of cigarettes smoked.

Fat distribution patterns with high WHRs are associated with risk factors—such as abnormal serum lipid levels, hypertension, and glucose intolerance—that have been linked to increased risks for coronary heart disease, diabetes, and increased mortality, the authors say.

Despite the weight gained by smokers who quit—5 pounds on average—their WHR did not increase significantly and was only one-fifth the increase expected for the weight they gained, the authors report. And although ex-smokers who started smoking again lost on average 2.2 pounds, their WHR increased instead of decreased. "These paradoxical changes in WHR indicate that there are harmful effects of cigarette smoking on the pattern of distribution of body fat. These facts introduce still another reason to suggest that the decision to initiate or to continue smoking to control body weight is unwise," the authors say. "The mechanisms that underlie the effects of cigarette smoking on the pattern of fat distribution are not known," the authors write. However, the knowledge that the cessation of smoking will not

result in significant worsening of the pattern of fat distribution, and that resumption of smoking among those who quit will not lead to improved fat distribution should encourage smokers to quit and to stay off cigarettes, they conclude.

JAMA February 25, 1989

ORAL STEROIDS WORSE FOR CHOLESTEROL LEVELS

Orally administered anabolic steroids may have a more deleterious effect on blood cholesterol levels than injections of the male sex hormone testosterone, says a study in the *Journal of the American Medical Association*.

The study compared the effects of orally administered stanozolol, an anabolic steroid, with intramuscular injections of testosterone on blood levels of proteins that help transport cholesterol through the body. The changes in the levels of lipoproteins following stanozolol treatment were much greater than those that followed testosterone therapy. These changes are associated with higher risks of atherosclerosis and coronary heart disease, say the authors, Paul D. Thompson, MD, and colleagues at Brown University Program in Medicine, Providence, RI.

Testosterone and its synthetic derivatives, anabolic steroids, have been used to manage osteoporosis, aplastic anemia, endometriosis, and other medical problems. But these agents also are being abused by an increasing number of athletes and others who want to improve athletic performance or physical appearance. Athletes who use these drugs have been found to have remarkable reductions in high-density lipoprotein (HDL) cholesterol concentrations and increase in a liver enzyme that may speed up the breakdown of HDL, the authors say. Studies have shown that high HDL levels help protect against heart disease, while elevated low-density lipoprotein (LDL) levels significantly increase the risk of heart problems.

Direct comparison between oral and injectable administration of the same steroid is not possible because no anabolic steroid is available for both oral and injectable use, the authors report. In their study, the authors measured lipoprotein cholesterol concentrations of 11 male weight lifters who received either oral stanozolol or intramuscular testosterone treatment for a six-week period. After a six-to nine-week "washout" period, the subjects were switched to the other therapy and their lipoprotein levels measured.

HDL cholesterol concentration was decreased 33 percent during stanozolol treatment, but decreased only

9 percent when the subjects were on testosterone, the authors report. In addition, LDL cholesterol increased 29 percent on stanozolol compared with 16 percent with testosterone.

Oral steroids are different from injectable steroids in that they have been chemically modified to resist rapid metabolism as they pass from the digestive tract through the liver. The authors believe that the more deleterious effects of stanozolol on lipoprotein levels may result either from this modification or from a higher concentration in the liver that results from oral administration. When prolonged treatments with androgenic or anabolic steroids are required for appropriate therapeutic indications, intramuscular testosterone may be preferable to oral agents, they conclude.

JAMA February 24, 1989

GLUCOSE CONTROL AND RENAL, RETINAL DIABETES COMPLICATIONS

A report in the *Journal of the American Medical Association* underscores the importance of good long-term blood glucose control in averting two major complications of insulin-dependent diabetes —retinal and kidney damage.

The study, by H. Peter Chase, MD, of the University of Colorado Health Sciences Center, Denver, and colleagues, found that diabetics with good long-term glucose control (blood sugar levels within 1.33 times the upper limit of normal) were far less likely to show signs of renal damage and retinopathy than those with poor long-term control (blood glucose values more than 1.5 times the upper limit of normal).

The study followed up 230 subjects with insulin-dependent diabetes, checking their glycohemoglobin (blood glucose) levels and evaluating them for microalbuminuria and retinopathy. Glucose control was the major variable relating to signs of kidney damage; duration of diabetes was a lesser factor. Duration of diabetes was the most significant variable relating to evidence of eye disease, followed in importance by glucose control and age, the study reports.

"It is clear," the authors say, "that both (glucose levels and duration of diabetes) are important in evaluating the risk for a given patient," the authors say.

"One explanation for this difference is that the kidneys must continually handle the increased glucose load and the increased filtering pressure that results from elevated glucose levels," the researchers write. "The endothelial membranes of the eye may act as more of a 'passive bystander,' affected by time."

Study subjects with poor long-term glucose control had 3.6 times the prevalence of microalbuminuria and the 2.5 times the prevalence of significant retinal damage than found in subjects with good long-term control, the authors report. In fact, say the authors, no patients whose mean blood glucose value was consistently within 1.1

times the upper normal limit showed evidence of retinopathy or renal damage. In contrast, when the mean glycohemoglobin value was more than 50 percent over the upper limit of normal, 29 percent of 82 subjects studied had microalbuminuria and 37 percent had significant retinopathy.

"Attempting to prevent the retinal and renal complications of (insulin-dependent diabetes) with good glucose control should be more effective than trying to reverse complications after they develop," the authors conclude.

JAMA February 25, 1989

SMOKING AND CAROTID ATHEROSCLEROSIS

Cigarette smoking is a strong, independent risk factor for the build-up of atherosclerotic plaque in the carotid artery, something that could lead to stroke, a study in the *Journal of the American Medical Association* says. This link exists even after other key risk factors, such as hypertension and age, are taken into account, say authors Grethe S. Tell, DPhil, of the Bowman Gray School of Medicine, Winston-Salem, NC, and colleagues. But the authors say their study, which used ultrasound to evaluate the carotid arteries in nearly 1,700 patients, also suggest carotid atherosclerosis may progress more slowly in those who quit smoking than in those who continue—the first report showing such a positive effect of giving up cigarettes. They also say race and sex were not significant variables in the smoking-atherosclerosis link, indicating "the effect of smoking is universal and that all subgroups of the population may benefit from not smoking."

JAMA February 24, 1989

SELENIUM LEVELS RELATED TO HEART ATTACK?

Low levels of selenium might play a role in the development of acute myocardial infarction (MI), a report in the *Journal of the American Medical Association* suggests. The study, by Frans J. Kok, PhD, of the Erasmus University Medical School, Rotterdam, the Netherlands, and colleagues, looked at selenium levels in plasma, erythrocyte and toenail samples from 84 heart attack patients and 84 healthy controls. Mean concentrations of all selenium measurements were lower in the patients than in the controls; except for plasma selenium levels, the differences were statistically significant, the authors say. What's more, heart attack risk tended to increase as toenail selenium levels decreased, even after adjusting for other MI risk factors. "Because the toenail selenium level reflects blood levels up to one year before sampling, these findings suggest that a low selenium status was present before the infarction and, thus, may be of etiologic relevance," the study says.

JAMA February 24, 1989

DIABETIC RETINOPATHY RISK

Two studies in February's *Archives of Ophthalmology* underscore the need to closely monitor diabetics for the development or worsening of retinopathy, a potentially serious degeneration of the retina. The reports, by Ronald Klein, MD, MPH, and colleagues at the University of Wisconsin Medical School, Madison, look at the four-year incidence and progression of diabetic retinopathy in a large population-based sample. Among insulin-taking diabetics diagnosed before age 30, 41 percent suffered a worsening of retinopathy over the four years. The study also confirms that the retinopathy risk increases after age 12 and levels off after 20 years of diabetes. But the data also "clearly indicate the risk of retinopathy worsening in a short time interval (four years) in...people with older-onset diabetes, a group previously thought to be relatively protected from retinopathy," the authors say. These patients, diagnosed after age 30, "make up the largest proportion of diabetic patients in the United States, (and) need examination when diabetes is first diagnosed and regular follow-up," they say.

NEW COMPLICATIONS OF COCAINE ABUSE

There are numerous reports detailing the destructive effect cocaine can have on the nasal septum but a report in February's *Archives of Otolaryngology-Head and Neck Surgery* describes a new complex of even more serious cocaine damage. The report, by Harold L. Deutsch, MD, and D. Ralph Millard, Jr., MD, of the University of Miami School of Medicine, says this complex consists of nasal collapse, septal perforation, retraction of the palate, and ulceration of the pharyngeal wall, with resulting effects on the voice, swallowing and eating. The authors describe three cocaine-abusing patients who sought treatment for these symptoms; two cases involved cocaine snorting and the other packing the drug into the nostrils. A literature review revealed no other reports describing cocaine-caused damage to the palate and pharynx, the authors say. The report describes one case in detail, saying "once it has been determined that the patient has abstained from cocaine use and the ulcerations have healed to a stable end point, reconstructive surgery will be attempted."

PREGNANCY OUTCOME RISKS NOT INCREASED BY ASYMPTOMATIC HIV INFECTION: STUDY

Pregnant women infected with human immunodeficiency virus (HIV) but asymptomatic for AIDS may not be at an increased risk for adverse pregnancy outcomes, other than the chance they will infect their babies with HIV, says a study in the *Journal of the American Medical Association*.

The study, comparing infected and uninfected pregnant intravenous drug users at a New York City methadone clinic, also showed pregnancy did not appear to accelerate the progression of HIV disease. In addition, pregnancy rates and the incidence of elective abortion were not different between the two groups, say authors Peter A. Selwyn, MD, MPH, of Montefiore Medical Center, Bronx, N.Y., and colleagues.

There were 125 pregnancies among the 97 women studied during the 28-month study period; 52 occurred among 39 asymptomatic HIV-infected women and 73 among 58 uninfected women. Eleven (28 percent) of the infected women and 15 (26 percent) of the uninfected women had two or more pregnancies. None of the HIV-infected women had advanced HIV-related disease at entry into the study, and only one developed an AIDS-associated disease (an oral yeast infection) during pregnancy, the authors report. Except for the increased incidence of bacterial pneumonia (3 cases) and a trend toward breech births among HIV-infected women, they found no differences between groups in the occurrence of problems either during pregnancies, as birth, or during the neonatal period.

The study reports only on problems other than HIV infection affecting the newborn. Babies born to mothers in both groups were tested for HIV, but the incidence of perinatal HIV transmission will be reported in a separate study.

Female IV drug users constitute the largest category of women with AIDS and most likely represent the largest population of HIV-infected women in the United States, the authors say. They caution, however, that their findings are preliminary and are likely to be more generalizable to women in early stages of HIV infection than to those with more advanced disease.

The pregnancy rates noted among the study subjects suggest there is little difference in reproductive activity between infected and uninfected IV drug abusers, the authors say. "The frequent occurrence of pregnancy, as well as the common observation of repeated pregnancies, supports clinical observations that contraception is an uncommon practice in this population. These findings have important implications for reproductive counseling and attempts to prevent perinatal transmission of HIV." They also say elective abortions were comparable between infected and uninfected groups, suggesting "knowledge of such status may not be a determining factor in decisions to terminate or continue pregnancies."

A related report in *JAMA* describes 20 previously unpublished cases of women with AIDS who died during pregnancy or within one year after its termination. "The interval between diagnosis of AIDS and the death of these women ranged from one day to 15 months, with a mean interval of 113 days," write the authors, Lisa M. Koonin, MN, MPH, of the Centers for Disease Control, Atlanta, and colleagues. All pregnancies had some obstetric complication and all the known live births occurred prematurely.

"Overall, these poor outcomes may have been associated with inadequate prenatal care, poor nutritional status, the presence of a chronic debilitating disease such as AIDS, and other health problems that are

characteristic of this largely drug-abusing population," the authors conclude. Prospective case-control studies are needed to determine the relationship between pregnancy and AIDS, they add.

In an accompanying editorial, Sheldon H. Landesman, MD, Howard L. Minkoff, MD, of State University of New York Health Science Center, Brooklyn, N.Y., and Anne Willoughby, MD, MPH, of the National Institutes of Health, Bethesda, Md., advise all clinicians involved in reproductive health—family planners, gynecologists, obstetricians, and midwives, particularly in communities in which HIV and other STDs (sexually transmitted diseases) are endemic—to "focus their professional energies toward decreasing the morbidity wrought by unsafe sexual practices and the STD epidemics they create. The importance of safer sexual practices must be routinely reinforced as part of the primary care of women."

JAMA March 3, 1989

STUDY: NICOTINE GUM OF LITTLE LONG-TERM HELP TO SMOKERS

Nicotine gum, provided with brief intervention counseling in general medical practice, does not appear to significantly improve the long-term rate at which smokers give up cigarettes, says a study in the *Journal of the American Medical Association*.

In a randomized, placebo-controlled study of 315 smokers who attended a family practice clinic and wished to quit smoking, little difference was found at the end of one year between the cessation rate of those who received nicotine gum and those given placebo gum, say the authors, John R. Hughes, MD, of the University of Vermont College of Medicine; and colleagues. Each patient received brief smoking cessation advice lasting 29 to 35 minutes from a physician and a nurse, including a slide presentation and written materials. Each also had a single follow-up visit a week after cessation lasting 12 to 20 minutes, the authors report.

At one- and six-month follow-up visits, about 10 percent more subjects in the nicotine gum group remained off cigarettes than in the placebo group. However, at the one-year follow-up session, there was no statistically significant difference in the abstinence rate between those on nicotine and those on placebo gum, they report. After taking marital status and income into account, 7 percent of those who received placebo gum and 10 percent of those on nicotine gum reported continuous abstinence for 11 months. These results were confirmed by reports from appointed observers and by biochemical tests.

The study sample size was too small to reliably measure quitting rate differences less than 10 percent, the authors report. However, a difference this small would not justify the use of nicotine gum, they write. "One could argue that, with such a small investment of time and such

a benign medication, such small increases in quit rates are sufficient to justify prescribing the gum. We believed that such small increases were not clinically significant given the cost of nicotine gum, its potential side effects (including dependency), and the fact that physician advice alone usually increases quit rates by 5 percent. Finally, a survey of 60 primary care physicians in our area indicated that the majority would not use a medication that increased smoking cessation rates by 5 percent."

The few previously conducted placebo-controlled studies of nicotine gum had several design problems and yielded contradictory results, the authors write. The one study reporting better quitting rates for those on nicotine gum used only highly motivated subjects, failed to biochemically verify abstainers, and did not report one-year smoking status. Hughes and colleagues say their study was designed to avoid these problems and to provide results more generalizable to the typical smoker-physician interaction that occurs in general medical practice. "The intensity of our intervention was the maximal feasible for a primary care practice according to a survey of local practitioners prior to the trial."

Based on their results and those of three of the four prior placebo-controlled trials, the authors conclude that, "when used with a nonselected group of smokers and a brief intervention in a general medical practice, the pharmacologic effects of nicotine gum to increase smoking cessation are either small or nonexistent." This conclusion is important, they say, because more than 99 percent of smokers who use nicotine gum are prescribed the gum during a brief visit with their physicians without taking part in a smoking cessation program, even though the Food and Drug Administration specifically states, in its approval for nicotine gum, that the gum should be used only with a behavioral modification program.

JAMA March 3, 1989

MANDATORY HIV REPORTING TESTING DETERRENT?

Mandatory reporting of human immunodeficiency virus (HIV) test results would reduce the number of homosexual men willing to be tested, a letter in the *Journal of the American Medical Association* suggests. Authors Susan M. Kegeles, PhD, and colleagues at the University of California, San Francisco, base the conclusion on a study of 574 homosexual men, most of whom had obtained HIV antibody testing. Most of the men said they would consent to HIV testing when seeking treatment for symptoms of AIDS or AIDS-Related Complex if reporting of the results to public health officials was not required, but only one-third said they would consent if results were reportable. Few would consent to testing if they were seeking treatment at a venereal disease clinic and results were reportable. While the vast majority of the men said they would consent to required testing if antidiscrimination laws were in place, most would avoid venereal disease treatment if testing

were required and no such laws were in place, as would one-third seeking treatment for symptoms of AIDS or ARC. "We must continue to concentrate our efforts on formulating policies and laws that help rather than hinder prevention efforts and access to health care," the letter concludes.

JAMA March 3, 1989

PHYSIOLOGICAL EFFECTS OF STANDING

Concerned about knee and leg aches? It might help to know where you stand, the "Questions and Answers" section of *JAMA* suggests. James J. Andonian, MD, of the Ford Motor Co., Dearborn, Mich., discusses "floor ergonomics" in response to a question about whether people who stand or work on concrete floors suffer more muscle and skeletal stress than those working on wood-beam floors. Researchers at the University of Michigan, he says, recently tested different floor types, ranging from concrete to matting of varying thicknesses, in 14 workers who stood during their entire work shift in a car-trim operation. Wood beams were not tested, but an attempt was made to simulate a broad range of conditions. Ratings of perceived hardness and discomfort in the feet, ankles, legs and back were highest for the concrete and lowest for the soft, thicker mats, although general fatigue ratings were higher with flooring that was too soft, he says. He also notes that the type of shoes worn, the tasks being performed, length of time standing and individual worker characteristics also play a role in floor ergonomics. "More research needs to be performed on the interaction between the worker and the surfaces on which he or she stands," he concludes.

JAMA March 3, 1989

MULTIPLE ABDOMINAL ORGAN TRANSPLANTS IN CHILDREN REMAIN UNPROVEN

Despite the deaths of the first four children to undergo multiple abdominal organ transplants, the new surgical procedure is a feasible treatment for young patients with damaged or missing small intestines and secondary liver disease, reports in the *Journal of the American Medical Association* say.

However, an editorial accompanying the two reports says that while enthusiasm for trying anything to save desperately ill children is understandable, this highly expensive, traumatic, and so far unsuccessful procedure should not be attempted on other children until it works in an animal model. Indeed, *JAMA's* "Medical News & Perspectives" section reports that the lead author of one of the two studies, after a more recent unsuccessful attempt by his group, now says he will shelve the procedure until organ rejection-control techniques are improved.

The children described in the study received new livers, stomachs, pancreases, and intestines at medical centers in

Pittsburgh and Chicago. Two died soon after surgery. The others lived for 193 and 109 days, respectively, with new organs that allowed them to be gradually weaned from intravenous feedings. But both died of cancer of the lymph system, which the authors believe resulted from the immunosuppressive drugs used to prevent organ rejection. Still, they say in their reports, the fact that the transplanted organs functioned for a time is encouraging, and that further cautious trials of this procedure are inevitable.

The authors, Thomas E. Starzl, MD, PhD, and colleagues at the University of Pittsburgh Health Center, and James W. Williams, MD, and colleagues at Rush-Presbyterian-St. Luke's Medical Center, Chicago, say they found no evidence of rejection of the transplants or of graft-vs-host disease—a potentially fatal reaction where immune cells transplanted from the donor attack the patient's cells. Williams and colleagues used X-rays to eliminate these killer cells in the donor organs prior to transplant, while Starzl's group used monoclonal antibodies to locate and destroy them. Unlike the children in Chicago, those in Starzl's study had also received colon transplants.

Intestinal transplantation has never been successful in humans, Williams and colleagues note. However, the children in their studies had lost most or all of their small intestines, due to illness or accidental injury, and therefore could not absorb nutrients. Intravenous feedings that kept them alive caused fatal liver disease and they were near death at the time of surgery, the authors report. Although none of the children survived, the authors say their studies demonstrate that the multiple transplant procedure can be performed with reasonable assurance of early success, and that methods of dealing with long-term problems—such as treating or preventing lymphoma—should now be addressed.

In his editorial, however, Francis D. Moore, MD, of the Harvard Medical School, Boston, strongly disagrees. He criticizes the Chicago group's claims that "the procedure is well borne" and that "metabolically fragile children tolerate the operative procedure very well." He notes that there was 50 percent immediate mortality and that the two children who initially survived the operation developed infections and leaks where the grafts were attached, along with other complications. "If this is tolerating the operative procedure very well, one wonders what it would look like if the procedures were not well tolerated," he writes.

Moore also criticizes the "desperate remedy" rationalization for trying anything on the desperately ill. "This sort of hyperbolic 'desperate remedies' pressure on physicians and patients (and on the reading public) should be looked on with skepticism," he writes. "There must be some likelihood of success before the desperate remedy becomes more than a desperate search for an opportunity to try a new procedure awaiting trial." Moore notes that desperate and poorly performed transplants during the "great heart transplant epidemic" of 1968 and 1969, "cast a pall over heart transplantation that could only be removed by another decade of slow plugging work by a few conscientious and experienced groups."

Moore also notes that either study mentions the cost of the surgery and hospitalizations. "We have here a total of about 295 days of the most expensive form of hospitalization known to humanity. The cost estimate of \$4,000 to \$5,000 per day is probably low," he writes. "Who carried this burden? Was it from research grants? Was it from family or friends, was it red ink for the hospital, or did the government somehow assist through one or another of its programs? This information would have been helpful to the reader."

"There can be no question that this procedure should be withheld from other patients for the immediate future, until such time as these two research groups (or others working in this field) have perfected an animal model," he writes. "Such an animal model has been absolutely essential to the development of all other forms of vascularized organ transplantation... There must be a rationale on which the desperately ill patient may be offered not merely pain, suffering, and cost, but also a true hope of prolonged survival (without lymphoma)."

JAMA's Medical News report describes a third attempt at multiple abdominal organ transplantation by Starzl's group on a 3-year-old girl last November. After numerous complications following surgery, she died in January of the same lymphoma that killed the two other children who initially survived the procedure. Starzl says his group will temporarily suspend further transplant attempts until better ways to control organ rejection can be found, the report says.

The report also describes a more successful series of abdominal organ transplants pioneered by Starzl's group that involved adults. Thirteen patients near death from liver, pancreatic, or duodenal cancer, have each received a new liver, pancreas, and duodenum, the report says. Unlike the children, the adults were able to keep their own small intestines, which the researchers say may be a factor behind the greater success of this procedure. Eleven of the patients have survived, one as long as six months, and all appear to be cancer-free so far. According to the *JAMA* report, Starzl says the knowledge gained from performing multiple abdominal organ transplants in children had helped them pioneer this procedure, which at least for now appears to be successful.

JAMA March 10, 1989

AMA PANEL CLOSELY DIVIDED ON GASTRIC RESTRICTION SURGERY

An AMA science review panel is closely divided on the safety and effectiveness of two gastric restriction procedures often used to treat morbid obesity, says a report in the *Journal of the American Medical Association*.

The Diagnostic and Therapeutic Technology Assessment (DATTA) panel evaluated the safety and effectiveness of gastric bypass surgery, which is designed to decrease food absorption, and vertical-banded gastroplasty, or "stomach stapling," in which the stomach is

partitioned to restrict energy intake.

When asked about gastric bypass as an adjunctive therapy to diet, exercise and behavior modification to treat patients 100 pounds or 100 percent over their optimal weight, 16 of 38 expert panel members considered the procedure to be established as safe, and 15 called it investigational. Five called it unacceptable and two said its safety was indeterminate. When asked about the procedure's effectiveness, 17 of 38 panel members considered it established, 16 called it investigational, four said it was unacceptable and one indeterminate.

Twenty-one of the 39 panel members evaluating the safety of vertical-banded gastroplasty called the procedure established, 15 called it investigational, two said it was unacceptable and one considered it indeterminate. On the issue of effectiveness, 18 of 39 voted for established, 16 said investigational, two said unacceptable and three indeterminate.

When the panel first reviewed gastric restrictive surgery in 1984, the report says, "there was no consensus on whether the safety and effectiveness of gastric bypass and gastroplasty were established or investigational. The panelists remain closely divided on this issue. Both the literature and the panelists' comments pointed out the importance of patient selection criteria and long-term follow-up to evaluate both the safety and effectiveness of these two procedures."

JAMA March 10, 1989

CAFFEINE AND ARRHYTHMIA

Heart disease patients are often warned about the potential harmful effects of caffeine, but this advice "is based primarily on anecdote and folklore," says a report in the March *Archives of Internal Medicine*. The study, by Thomas B. Graboys, MD, of the Harvard School of Public Health, Boston, and colleagues, finds no evidence that a modest dose of caffeine causes heart rhythm disturbances, "even among patients with known life-threatening arrhythmia." The study involved 50 such patients given either decaffeinated coffee or decaf with 200 mg of caffeine added. Continuous electrocardiographic monitoring showed no differences between the two groups "in either individual or group data on total or repetitive ventricular arrhythmia," the authors say. They acknowledge that there probably are caffeine-sensitive patients who "will experience an aggravation of ventricular or atrial arrhythmias" and need to be individually identified, but say available data suggest that this group "is indeed small."

ULTRAVIOLET LIGHT EXPOSURE AND CATARACT RISK

Ultraviolet B radiation (UV-B), the portion of sunlight implicated in skin cancer, also may be an important risk factor for a particularly disabling type of cataract, a study

in the March *Archives of Ophthalmology* suggests. Posterior subcapsular cataracts (PSC) are relatively infrequent among cataract types but account for a disproportionate share of cataract surgery cases (an estimated 40 percent in the United States), say authors Tom Bochow, MD, MPH, of the Johns Hopkins University, Baltimore, and colleagues. The study, which looked at various potential PSC cataract risk factors, involved 168 PSC cases and 168 matched controls. The authors say a history of relatively high exposure to UV-B was associated with increased risk of PSC cataracts; they also reconfirmed the previously reported link between PSC and steroid use and diabetes. "If indeed UV-B is related to the pathogenesis of PSC cataracts, as this study strongly suggests, the wearing of hats and sunglasses could greatly reduce ocular exposure and possibly alter the development or progression of this disease," they say.

HTLV-I ASSOCIATED WITH CHRONIC MYELOPATHY

A French study in the March *Archives of Neurology* adds to the evidence suggesting that human T-lymphotropic virus type I (HTLV-I), the virus thought to cause adult T-cell leukemia, also may be involved in chronic myelopathy, or spinal disorders of unknown cause. Authors Olivier Gout, MD, of the Hospital de la Salpêtrière, Paris, and colleagues screened 167 neurologic patients for HTLV-I antibodies. Of 37 patients with chronic myelopathy, 10—all of whom had a form of spastic paralysis called tropical spastic paraparesis—tested positively for the virus. What's more, the authors say, a retrovirus similar to HTLV-I was isolated in five of these cases at various times during the course of the disease. Eight of these patients were born in areas where HTLV-I is endemic, the study notes. In such cases, it suggests, anti-viral therapy is merited using agents shown to inhibit in vitro activity of HTLV-I—including zidovudine (formerly AZT).

MATERNAL CIGARETTE SMOKING AND CLEFT LIP/PALATE RISK

Children whose mothers smoke during pregnancy run a higher risk of having cleft lip and/or cleft palate, suggests a study in the March *AJDC, American Journal of Diseases of Children*. Authors Muin J. Khoury, MD, PhD, of the Centers for Disease Control, Atlanta, and colleagues analyzed data from a population-based, case-control study of a variety of birth defect risk factors. Offspring of mothers who smoked cigarettes during the three months before or after conception were 60 percent more likely than those of non-smokers to have isolated (where the cleft is the only major defect) cleft lip with or without cleft palate, and twice as likely to have cleft palate, say the authors. No association was found between smoking and oral clefts linked to other defects. If

smoking does play a role in causing oral clefts, the authors conclude, "it probably does so for a selected subgroup or oral clefts that will have to a characterized further." They also suggest that "a small fraction of the population at large may be biologically susceptible to a teratogenic effect of smoking."

DUTY TO WARN ABOUT TRANSFUSION RISKS

Blood banks and transfusion services traditionally have not been held liable in cases where patients contracted unavoidable transfusion-related diseases. But identification of new transfusion risks—such as AIDS—and "efforts to find new sources of compensation" may cause judges to develop new theories of liability, says a report in the March *Archives of Pathology and Laboratory Medicine*, a special issue highlighting the question of safety in transfusion practices. Author David E. Willett, JD, of the San Francisco law firm of Hassard, Bonnington, Rogers, and Huber, advises blood bank and transfusion service medical directors "to provide clinicians with information regarding current or emerging transfusion risks and alternative such as autologous transfusion, urging communication to patients when informed consent is obtained," he writes.

SAFETY OF PREGNANCY AFTER DISCONTINUATION OF ISOTRETINOIN

There have been a number of reports of congenital malformations due to fetal exposure to the drug isotretinoin (Accutane), a vitamin A-derivative prescribed to treat acne. But a study in the March *Archives of Dermatology* suggests women who complete or discontinue isotretinoin therapy prior to pregnancy are not at a statistically significant risk of such fetal malformation or spontaneous abortion. The report, by Wanju S. Dai, MD, DrPH, and colleagues at Hoffmann LaRoche, Inc., Nutley, NJ, the drug's manufacturer, is based on a study of 88 cases in which conception occurred after isotretinoin treatment was discontinued. The incidence of both spontaneous and missed abortions from all pregnancies was 9.1 percent, and the incidence of congenital malformations among live births was 5 percent. "The incidence rates for both these outcomes were not significantly different from the rates reported for women of reproductive age in the general population. In addition, the malformations reported were not characteristic of retinoic acid-induced congenital anomalies," the authors say.



VASOTEC

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx (likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered. (See ADVERSE REACTIONS.)**

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General:* **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Osmotic reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298/ patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostatic hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: Hypertension: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) and with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. JVS18R(815)

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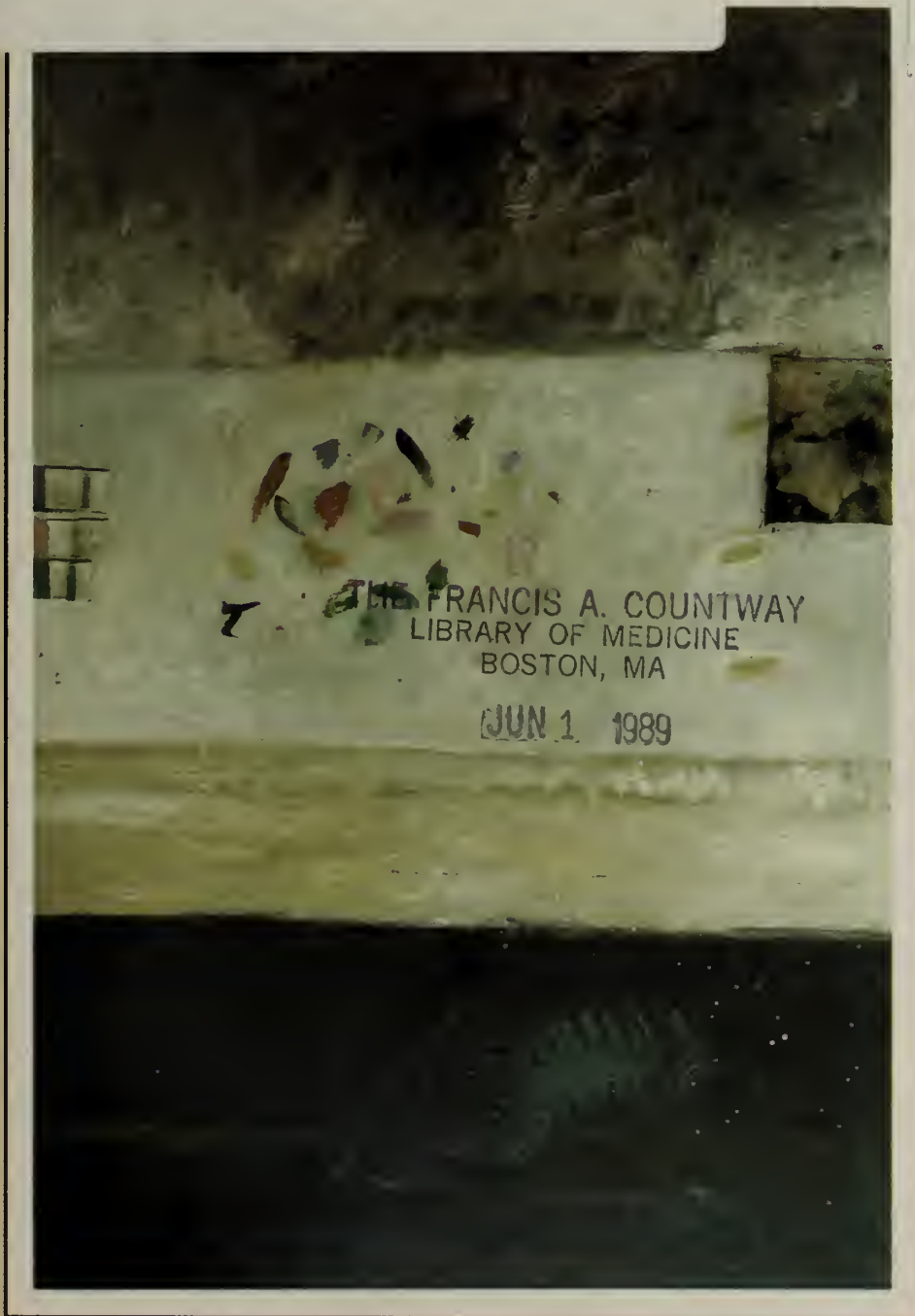
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even smaller
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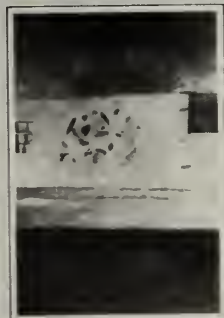
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ASOCIACION MEDICA DE PUERTO RICO
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Nuestra Portada

NUESTRA PORTADA

Trapos, Tubos y Paleta. Collage en aceite sobre acrílico del artista Ralph De Romero. El autor de la obra nació en Nueva York en 1940, de padres puertorriqueños. 1940 a temprana edad vino a la Isla donde permaneció hasta 1961 cuando se trasladó a Nueva York a cursar estudios en el Institute of Music Art. En 1965 se traslada a la Universidad de Puerto Rico donde estudia bajo la tutela de Balossi, Bonilla, Norat, Carlos Marichal y Osiris Delgado. Su deseo de superación constante lo lleva de nuevo a su ciudad natal donde es discípulo del profesor Edgar Levy en el Pratts Institute durante los años 1967 al 1970. Luego marcha a México y por tres años estudia la técnica del muralismo en la capital azteca. Finalmente regresa a Puerto Rico y se radica en Ponce donde hace "excursiones" en toda la Isla en experimentación artística.

Las obras de De Romero han participado en exposiciones individuales y colectivas en Puerto Rico desde 1965. Luego de ella le han seguido exposiciones en galerías de renombre de Nueva York, San Francisco, Oakland, Corea del Sur, Japón y Madrid, España.

El óleo que aparece en nuestra portada fue terminado en 1985 y su publicación ha sido posible gracias a la gentileza del autor y de la Sra. María Rechany. Otras obras de De Romero pueden apreciarse en La Casa Amarilla en la Calle Navarro de Hato Rey.

ESTUDIOS CLINICOS

Mamoplastía de Reducción: ¿Salud o Belleza?

Resumen: Existe la impresión errónea en el campo de la salud en Puerto Rico que la mamoplastía de reducción es una operación puramente cosmética. Creen los autores que la hipertrofia mamaria afecta la salud física y mental de la mujer puertorriqueña y que la mamoplastía de reducción es el tratamiento indicado.

Se hace un estudio de investigación. Como parte de la metodología, se prepara un instrumento tipo cuestionario que se le administra a 54 mujeres postoperadas. Sale a relucir en el estudio que el 98% tuvo mejoría de síntomas, y el 90% le recomiendan la operación a otras. Prueba este estudio la hipótesis de que la hipertrofia mamaria afecta la salud física y mental y que la mamoplastía de reducción es la solución de este problema. Reflejó, además el estudio que un exceso de 250 gms. es suficiente para dar síntomas de hipertrofia mamaria.

La mamoplastía de reducción de acuerdo a Rees¹ es una operación que en la mayoría de los casos se lleva a cabo por indicaciones de salud. Existe, sin embargo, la impresión en el campo de la salud de que esta cirugía se realiza más por razones estéticas. Esta forma errónea de pensar surge de ideas arcaicas. Para el 1967 el investigador principal de este estudio publicó sus primeras experiencias con la cirugía del seno, la cual tituló "*Mammary Cosmetic Surgery*".² En dicho artículo se reflejaba la forma de pensar que predominaba para esa época sobre este tipo de cirugía. Desde mucho antes, en los orígenes de la cirugía plástica del seno, Thorek³ y Passot⁴ hablaban también de la reducción del seno como una operación estética.

Contribuye a la incertidumbre de si la reducción del seno es por salud o por belleza el hecho de que la nomenclatura es confusa. En el pasado los términos usados eran entre otros: hipermastia, gigantomastia, macromastia y mastoplasia para referirse al engrandecimiento no maligno del seno femenino. Luego Letterman y Schuster⁵ desarrollan una nomenclatura en la cual establecen que hipertrofia mamaria es el término correcto. Para determinar la cantidad en exceso del tejido glandular y el

lipofibrótico que ocasionan la hipertrofia mamaria, se ha recurrido al método retrospectivo, el cual consiste en analizar los pesos de especímenes removidos durante la mamoplastía de reducción.

Cuadro Clínico de la Hipertrofia Mamaria

Clínicamente ya es aceptado que las pacientes con hipertrofia mamaria desarrollan dolor del cuello, senos, hombros, espalda torácica, espalda lumbar, úlceras y además marcas de presión en los hombros causadas por el manguillo del sostén, dermatitis debajo del seno y parestesias de los dedos ulnares (Rees, Penn, Stark, Converse).^{1, 6, 7, 8} Los signos y síntomas señalados en la literatura se ven a diario dentro de las quejas de las pacientes que forman parte del universo utilizado para propósito de éste estudio. De igual forma, según Conway,⁹ la cifosis torácica es común así como los cambios en el sistema esquelético según lo refieren también Letterman y Schuster.⁵ Estos enfatizan los daños que hace el exceso de peso, además de presentar el síndrome de presión coracóidea que explica por qué muchos de los pacientes con hipertrofia mamaria desarrollan parestesias del lado ulnar de la mano. Debido a la hipertrofia mamaria pueden ocurrir cambios neurológicos, los cuales son documentados por Kaye.¹⁰

A través de la revisión de literatura se ha notado abundancia en las publicaciones sobre la técnica de mamoplastía de reducción pero, una escasez en los estudios del cuadro clínico de hipertrofia mamaria. El estudio realizado por Strombeck¹¹ reflejó que un 83% de sus pacientes, a los cuales les había hecho cirugía de reducción de senos, demostraron estar satisfechos con la operación. Nos señala además, tener la impresión, que en las pacientes a las cuales se les ha removido más de 500 gramos por seno, el alivio es mayor. Esta conclusión lleva a muchos cirujanos plásticos y por ende, a compañías de seguros de salud a pensar que sólo la remoción de un exceso de 500 gms. o más es indicativo de hipertrofia mamaria. Encontramos en Puerto Rico mujeres de escasa estatura con hipertrofia mamaria en las cuales al revisar sus expedientes médicos el exceso era menos de 500 gms. De acuerdo con nuestra experiencia, con pacientes de 250 gms. de exceso en adelante ya se notan síntomas de hipertrofia mamaria. Las compañías de seguros de salud locales rehúsan cubiertas a estas pacientes. Para remediar este discrimen hemos diseñado la tabla de clasificación que presentamos a continuación (tabla I).

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Tabla I

Clasificación de la hipertrofia mamaria de la mujer puertorriqueña

Especimen por seno	Estatura	Peso de la paciente
A. 250 gms.	5'	<100 lb.
B. 350 gms.	5' 1" - 5' 2"	101 - 140 lbs.
C. 450 gms.	5' 3" - 5' 4"	141 - 160 lbs.
D. 500 gms.	5' 5"	>161 lbs.
E. 501 gms.	Todas	

Esta clasificación nos sirve de guía para efecto de determinar elegibilidad en la cubierta de seguros de salud en la mujer puertorriqueña. En los casos que se extirpan de 250 gms. y que usualmente son asintomáticos se clasifican bajo el diagnóstico de ptosis mamaria. Esta condición es usualmente reconocida como un problema puramente estético. De 251 gramos en adelante es indicativo de hipertrofia mamaria tomando en consideración el peso y estatura promedio de la mujer puertorriqueña.

Nuevamente en el 1972 Strombeck¹² realiza un estudio en el cual recopila datos concernientes a 12 años de su experiencia. Los hallazgos del mismo revelaron que 82% de los pacientes manifestaron sentir desde una gran mejoría a desaparición completa del dolor ocasionado por el peso exagerado de los senos.

Ante la impresión errónea que existe aún en Puerto Rico, por parte de algunos proveedores de la salud, sobre el tipo de cirugía ya antes mencionado, surge la inquietud en los investigadores de estudiar el problema de si la "mamoplastia de reducción contribuye a la salud o a la belleza."

Las siguientes hipótesis fueron formuladas para propósito de la investigación:

- A- La hipertrofia mamaria afecta la salud física y mental.
- B- La mamoplastia de reducción para la condición de hipertrofia mamaria contribuye a la salud física y mental.

La Organización Mundial de la Salud en su definición señala que la salud es el óptimo nivel de bienestar físico, mental y social y no meramente la ausencia de enfermedad dentro del marco de referencia de la visión holística.¹³ Tomando en consideración esta definición de la Organización Mundial de la Salud, se lleva a cabo el estudio desde una perspectiva holística aplicando la siguiente metodología.

Metodología

Se diseñó un instrumento tipo cuestionario el cual constaba de dos partes. La primera recopilaba datos demográficos y la segunda parte constaba de una serie de premisas en forma de selección múltiple. Ambas partes constituían un total de 20 premisas. El mismo fue administrado de abril a julio de 1988.

Para propósitos del estudio se toma como muestra a cincuenta y cuatro (54) pacientes post-operados selec-

cionados al azar consecutivamente. Las mismas habían sido diagnosticadas con hipertrofia mamaria y se les había realizado mamoplastia de reducción. Se aplicó la fórmula de universos conocidos $n = \frac{NZ^2 6^2}{(N-1) E^2 + 6^2}$ para determinar el tamaño de la muestra con un 95% de confiabilidad. El análisis estadístico se llevó a cabo mediante el sistema "Statistical Package for the Social Sciences" versión 2.1 (SPSS-X2.1).

Resultados

Al analizar la frecuencia observada se obtuvo los siguientes datos (tabla II). La edad promedio de los sujetos encuestados era de 35 años. Un 83% de los sujetos estudiados refirieron que antes de la operación estaban conscientes de que la mamoplastia de reducción les ayudaría a mejorar la postura, realizar las tareas del diario vivir más eficazmente y lucir mejor su ropa (tabla III). En nuestra cultura se sabe que la mujer está

TABLA II
MAMOPLASTIA DE REDUCCION
SALUD ó BELLEZA

EN QUE GRUPO DE EDAD SE ENCONTRABAN ANTES DE LA REDUCCION:

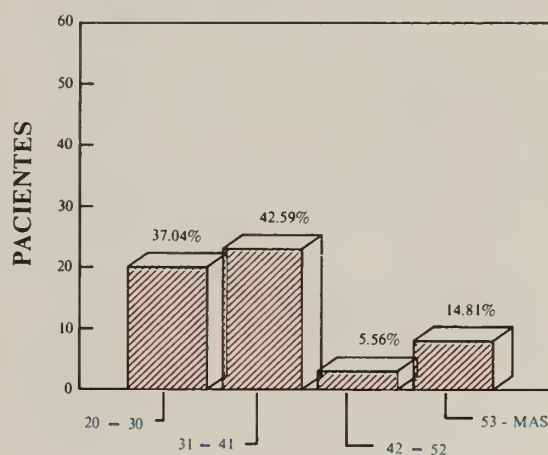
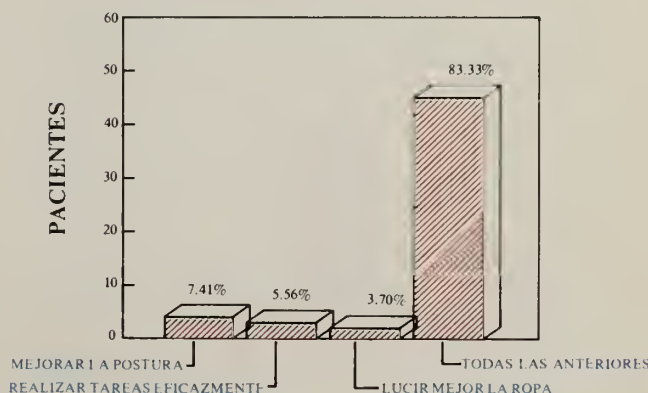


TABLA III
MAMOPLASTIA DE REDUCCION
SALUD ó BELLEZA

ESTABAN CONCIENTES DE QUE LA CIRUGIA LAS AYUDARIA A:



muy orgullosa de su cuerpo, sin embargo 80% de los sujetos manifestaron que antes de la mamoplastia de reducción sentían vergüenza de su cuerpo (tabla IV). Antes de la operación un 90.7% refirieron sentirse cansadas y un 92.5% expresaron que el sostén le ocasionaba presión en los hombros (tablas V - VI).

Para el 98% de la población estudiada el dolor de los hombros, espaldas y otras áreas afectadas por el tamaño de los senos había disminuido o desaparecido en su totalidad luego de la mamoplastia de reducción. Un 76% indicó que el dolor anteriormente indicado había desaparecido por completo (tabla VII). Un 98% de los sujetos indicó que recomendarían la operación a cualquier que conocieran con el problema de hipertrofia mamaria. Estos hallazgos reflejaron que en el 91% de los sujetos la razón principal por la cual se hizo la mamoplastia de reducción fue la de eliminar el dolor que el tamaño del

seno le ocasionaba en la región de espalda, hombros y pecho.

La industria de seguros de salud en Puerto Rico según Muñoz¹⁴ tenía un volumen de \$453.8 millones en 1985-86 y sigue creciendo a pasos agigantados. Sin embargo, los hallazgos encontrados indican que el 48% de los sujetos tenían un seguro de salud pre pagado, pero ninguno de los planes locales estaba representado. El 40.7% pagaron la cirugía de contado y 7.4% pagaron coaseguro. Esto nos da un total de 48.1% que hicieron pagos de su bolsillo (tabla VIII). La industria de seguros de salud utiliza las normas de coaseguro y deducible para controlar la sobreutilización. Esto asume que el que está dispuesto a incurrir en los gastos es porque considera que su condición es meritoria y por lo tanto justificada. Tenemos en la muestra un porcentaje alto de sujetos que estuvieron dispuestos a costear la operación a pesar de no tener cubierta de seguro de salud. Es obvio que los seguros de salud de estas mujeres no están llenando las necesidades para minimizar el cuadro clínico que ellas sufren.

TABLA IV

MAMOPLASTIA DE REDUCCION SALUD ó BELLEZA

ANTES DE LA REDUCCION DE SENOS SE SENTIAN:

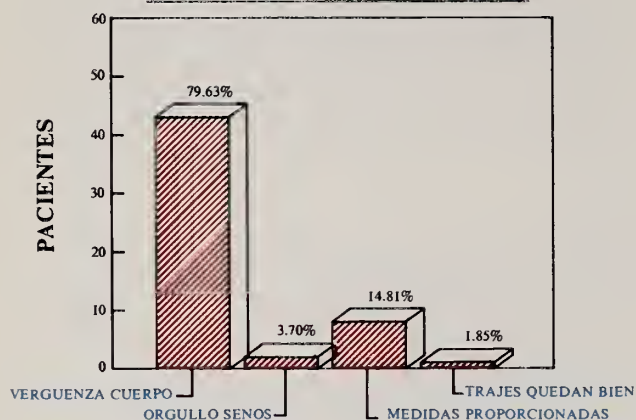


TABLA V

MAMOPLASTIA DE REDUCCION SALUD ó BELLEZA

EL PESO DE LOS SENOS LAS HACIAN SENTIR:

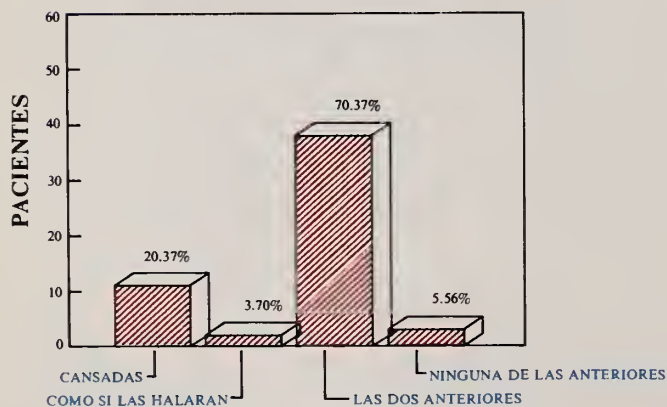


TABLA VI

MAMOPLASTIA DE REDUCCION SALUD ó BELLEZA

ANTES DE LA CIRUGIA EL SOSTEN LE PROVOCABA:

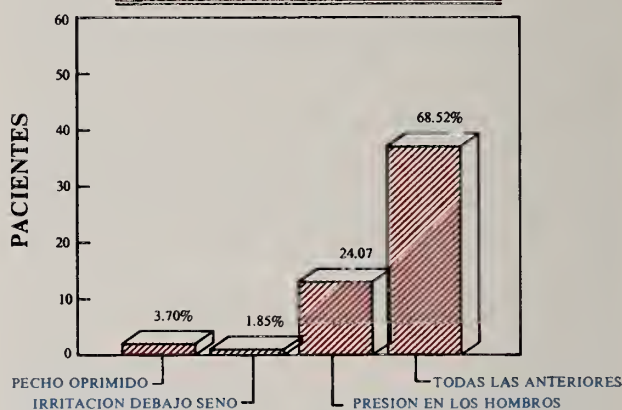


TABLA VII

MAMOPLASTIA DE REDUCCION SALUD ó BELLEZA

LUEGO DE LA REDUCCION DE SENOS:

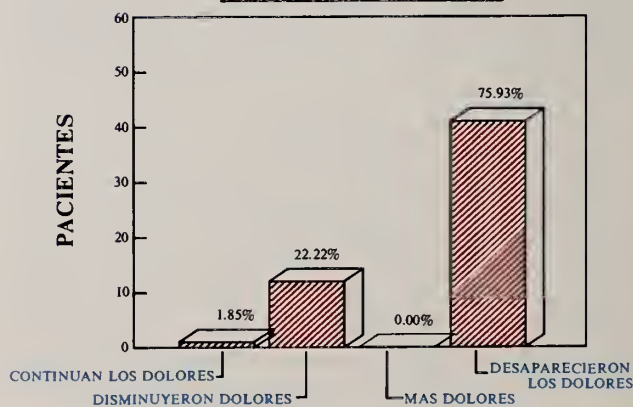
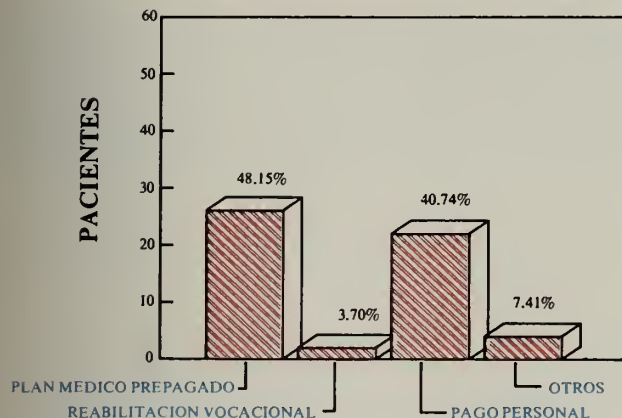


TABLA VIII

MAMOPLASTIA DE REDUCCION SALUD ó BELLEZA

LA REDUCCION DE SENOS FUE COSTEADA POR:



Resumen y Conclusión

Se concluye que las hipótesis establecidas han sido debidamente comprobadas. Los hallazgos de este estudio indican que la hipertrofia mamaria afecta la salud física y mental de la mujer puertorriqueña. Refleja, además, que el 98% de los sujetos recomendarían la mamoplastia de reducción a cualquier mujer que presente la condición de hipertrofia mamaria. Los porcentajes altos de mejoría de síntomas a la par con el alto grado de satisfacción de estos pacientes son indicativos de que la mamoplastia de reducción es el tratamiento adecuado para la hipertrofia mamaria.

Recomendamos que la clasificación presentada en la tabla I se utilice como uno de los parámetros para determinar elegibilidad. Se sugiere que los planes de seguros de salud acepten la hipertrofia mamaria como una condición médica y establezcan normas para cubiertas adecuadas con el fin de superar el estado de salud físico y mental de la mujer puertorriqueña que padece de hipertrofia mamaria.

Summary: There is the wrong idea among health providers in Puerto Rico that reduction mammoplasty (RM) is a purely cosmetic procedure. The authors believe that mammary hypertrophy (MH) is a health problem and that reduction mammoplasty is the indicated treatment.

A research program is devised using in its methodology a questionnaire which administered to 54 postoperative female patients. The study shows that 98% had significant improvement of symptoms and 98% recommend the operation to their friends. Our research confirms the hypothesis that MH affects health and RM is adequate treatment. We also concluded that an excess of 250 gms. is enough to cause symptoms of MH.

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LISTA DE ANUNCIANTES

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Acute Appendicitis

A.S. Casanova-Díaz, MD, FACS

Acute appendicitis is practically always precipitated by obstruction of its lumen, be it by hyperplasia of the lymph follicles, fecaliths, inspissated barium, or tumors. Very rarely it is due to some other condition affecting the appendix. The relative prevalence of the type of obstruction, varies with the source of information,^{1, 2} but hyperplasia of the lymph follicles and fecaliths are the most common, the former most likely prevailing in young children. Fecaliths prevail in gangrenous appendicitis, (40%) and in gangrenous appendicitis with rupture (90%).²

The appendix is capable of continuing mucosal secretions in the presence of obstruction,² causing increase in intraluminal pressure, which is also augmented by rapid multiplication of the resident bacteria. This process at first leads to engorgement because of obstruction to the capillary and venules flow while the arterioles are still pumping blood; but eventually, if the process is continued, tissue necrosis (gangrene, perforation) ensues.

The initial distension of the organ, by visceral nerve stimulation, produces the vague, dull, diffuse pain in the mid-abdomen or epigastrium, and may stimulate peristalsis, so that some cramping may be superimposed on the visceral pain early in the course of appendicitis.² The eventual inflammatory process which follows involves the serosa of the appendix and the adjacent parietal peritoneum, causing the shift of the pain and the local tenderness and muscle guarding.

The diagnosis of acute appendicitis is usually made without the need of any elaborate process, just simply with a good history and a good physical examination.

The salient points in the history are:

A. Abdominal pain, usually not too severe, as a rule constant (though some cramping discomfort may be felt in the early beginning, as stated above). It starts as a rule in the epigastrium or in the periumbilical area, and later on, in from two to six hours, shifts to somewhere else in the abdomen, usually the right lower quadrant (RLQ), but it could be any other place, depending where the inflamed organ be located, it could be in the left lower quadrant (LLQ), the pelvis, the right upper quadrant (RUQ), etc. The presence of such a shifting pain should alert the examiner to the possibility of acute appendicitis, and that diagnosis should be entertained until otherwise proven, especially if accompanied by the second most important symptom: anorexia.

B. Anorexia. This is a very important symptom. The patient loses his desire to eat. If he is hungry, the diagnosis of acute appendicitis should be questioned, but not ruled out.

C. Nausea and/or vomiting. It is usually not severe, and mostly precipitated by the ingestion of solids or liquids. It is rarely continuous or severe.

D. Obstipation. As the peristalsis stops as results of the peritoneal irritation, the bowels do not move. However, being an acute process, the change in bowel habit may not be readily appreciable. For example, a patient who usually moves his bowels once a day, in the morning may develop acute appendicitis at noon, and if diagnosed in the evening and surgery performed soon afterwards, no change in bowel habit would have been observed.

Diarrhea may occur in certain cases, as will be mentioned below (retrocecal, and low lying pelvic appendicitis).

E. Fever. As a rule it is not too high, and may even be absent at the onset. It increases as the inflammatory process progresses.

The presence of high fever at the onset of the disease, may suggest another etiology for the condition in question, such as pelvic inflammatory disease (PID), urinary tract infection, mesenteric adenitis, etc.

In regards to physical signs, the most important are:

A. Point tenderness. This is the most relevant sign. It will be detected directly over the place where the inflamed organ is located, usually the RLQ, but could be anywhere in the abdomen, such as the LLQ (in *situs inversus* or a long appendix extending to the left side), or deep in the pelvis (in which case the tenderness may be detected only on vaginal or rectal examination), which would occur when a long appendix hangs down into the pelvis; or in the RUQ if the tip of the appendix is there; etc.

B. Rebound tenderness, which could be direct (right over the place where the appendix may be) or referred, which is pain referred to a place other than where the pressure is directly applied. That place would be where the appendix is located, usually the RLQ.

C. Muscle guarding over the affected area, indicating peritoneal irritation, the same as the tenderness. Diffuse tenderness and diffuse muscle guarding suggest diffuse peritonitis and not a simple localized acute appendicitis.

D. *Fever*, already described under symptoms. It may be higher in young children.

E. *Absent or depressed peristalsis*, as mentioned under obstipation. In cases of retroileocecal appendicitis, as described below, there may actually be hyperactive peristalsis.

F. *Chills* --- rarely seen in uncomplicated acute appendicitis, and, if present, may point to another diagnosis, such as urinary tract infection. If associated with acute appendicitis, pyelophlebitis should be suspected, and immediate appropriate therapy should be started.

G. *Leukocytosis*, usually not too high (11,000 to 15,000). Acute appendicitis, though, may occur in the presence of a normal blood count. An elevated count indicates only that an infection (or inflammation) is present, but it does not say where.

The blood count, nevertheless, is an integral part or the evaluation for acute appendicitis, not necessarily to establish the diagnosis (except in doubtful cases, in which a rising white blood cell count, in the presence of some suggestive, but not striking abdominal signs may indicate appendicitis), but to determine the severity of the case, or to detect associated conditions which could require additional emergency treatment. For example, an extremely low white blood cell count could suggest the presence of significant granulocytopenia, or even agranulocytosis, while a very high count could mean leukemia, conditions which would indicate that the body defenses are low, and that ample and adequate antibiotic therapy should be started immediately and that the appendectomy should be performed without waste of time.

Also, if marked anemia is detected in the hemogram, in case of a young, previously healthy female, the diagnosis of gynecological bleeding, most likely ruptured ectopic pregnancy, should strongly be considered.

H. *Tachycardia*, rarely high unless there is an associated complication.

In the absence of definite local tenderness, but with the typical pain and anorexia present, retrocecal appendicitis should be suspected, in which case there should be some percussion flank or CVA tenderness. Also, in retrocecal appendicitis, some diarrhea may be present, due to irritation of the cecum. Diarrheas may also occur with a long appendix hanging low in the pelvis, irritating the rectosigmoid. In such a case, the vaginal and rectal examinations should be diagnostic.

An acutely inflamed appendix located behind the ileocecal area may show a bizarre picture, with the typical shifting pain and anorexia, but little local tenderness and guarding, and with a different type of pain added, crampy in nature, associated with more frequent vomiting, and with radiological evidence of low small bowel obstruction. Peristalsis may be quite active, even with rushes, in sharp contradistinction to the absent or depressed peristalsis of the usual acute appendicitis. In those cases (retroileocecal), the walled-off appendix covered by the terminal ileum and the posteriomedial wall of the cecum,

does not cause much peritoneal irritation, but causes pressure obstruction of the terminal ileum.

As to adjuvant studies which could help in the diagnosis of acute appendicitis, X rays are useful in three specific circumstances:

Table I

Differential Diagnosis of Acute Appendicitis

A. Gynecologic conditions

1. Pelvic inflammatory disease
2. Ruptured ectopic pregnancy
3. Ruptured Graafian follicle
4. Ruptured corpus luteum cyst
5. Torsion of ovarian cyst

B. Urological conditions

1. Ureterolithiasis (ureteral colic)
2. Acute pyelitis
3. Acute pyelonephritis
4. Cortical or perinephric abscess
5. Torsion of testicle
6. Acute epididymitis

C. Gastrointestinal conditions

1. Mesenteric adenitis
2. Meckel's diverticulitis
3. Regional enteritis (Crohn' disease)
4. Acute cecal diverticulitis
5. Focal hemorrhagic infarct of omentum
6. Intussusception
7. Ruptured peptic ulcer
8. Acute cholecystitis
9. Acute pancreatitis
10. Torsion or gangrene of epiploic appendage
11. Primary peritonitis
12. Henoch-Schonlein purpura

1. In a child (or an adult for that matter) who may have acute appendicitis but the findings are not quite typical, a flat plate of the abdomen, if it shows a radiopaque object (fecalith or inspissated barium) in the area of the appendix, is very helpful because it would suggest that the appendix is obstructed and is quite likely the cause of the symptoms, or it will probably become obstructed and inflamed in the near future, and, therefore, appendectomy is indicated for either therapy or reasonable prophylaxis.

2. When a retrocecal appendicitis is suspected, but the surgeon still has some doubts, a carefully done barium enema study will be helpful. If the appendix is the culprit, a retrocecal mass will be demonstrated and also cecal irritation.

3. In the case of retroileocecal appendicitis, as already stated above, flat X rays of the abdomen should show the radiologic picture of low ileal obstruction.

In conclusion, a patient with a history of constant abdominal pain, starting in the epigastrium or periumbilical area, and later on shifting to elsewhere in the abdomen, especially the RLQ, associated with anorexia, and showing point tenderness, also usually in the RLQ, has acute appendicitis until otherwise proven.

Summary: Acute appendicitis is discussed from the etiologic standpoint, symptoms and signs. The origin and the shift of the pain is explained. The importance of shifting pain, anorexia and point tenderness, is stressed. The altered picture seen in retrocecal, retroileocecal and low lying pelvic appendicitis is described and diagnostic measures pointed out. The limited, but very helpful radiologic findings in some cases are mentioned.

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PRUEBA DE EDUCACION MEDICA CONTINUADA

1. El síntoma más sugestivo de apendicitis aguda es:
 - (a) Nauseas y vómitos
 - (b) Obstipación
 - (c) Dolor periombilical o epigástrico que cambia de posición
 - (d) Dolor cólico
 - (e) Fiebre
2. El signo más sugestivo de apendicitis aguda es:
 - (a) Dolor al tacto localizado ("point tenderness")
 - (b) Leucocitosis
 - (c) Fiebre
 - (d) Ausencia de peristaltismo abdominal
 - (e) Taquicardia
3. Los siguientes son hallazgos frecuentes en apendicitis aguda, excepto:
 - (a) Dolor a la palpación
 - (b) Anorexia
 - (c) Escalofrios severos
 - (d) Febrícula
 - (e) Nauseas
4. La siguiente combinación debe sugerir apendicitis aguda hasta que se pruebe lo contrario:
 - (a) Fiebre alta y escalofrios
 - (b) Dolor cólico y vómitos repetidos
 - (c) Dolor epigástrico que cambia al cuadrante inferior derecho, asociado con dolor a la palpación en la misma area.
 - (d) Distensión marcada y diarreas.
 - (e) Todo lo mencionado

B. Cierto o Falso

5. La presencia de leucocitosis es indispensable para el diagnóstico de apendicitis aguda.
6. La presencia de asas de intestino delgado dilatadas no es compatible con apendicitis aguda.
7. La diarrea nunca ocurre con apendicitis aguda.
8. "Retortijones" (cólico intestinal) pueden ocurrir con apendicitis aguda.
9. Vómitos severos, persistentes, son típicos de apendicitis aguda.
10. Dolor a la palpación, difuso, en todo el vientre, es característico de apendicitis aguda.



EDUCACION MEDICA CONTINUADA

La Asociación Médica de Puerto Rico (AMPR) es una institución acreditada para ofrecer Educación Médica Continuada (EMC). La AMPR ha determinado que este ejercicio académico reúne los criterios para 1 hora-crédito de EMC categoría I para la Asociación Médica Americana y para la oficina de Reglamentación y Certificación de Profesionales de la Salud. Al final del año se enviará un Certificado de acuerdo al número de pruebas sometidas. Para obtener crédito favor de seguir las instrucciones que se detallan a continuación.

1. Leer el artículo detenidamente y seleccionar la contestación correcta a cada pregunta de la prueba en el espacio que se provee para ello. Cada pregunta tiene una sola respuesta.

2. Retener una copia de la hoja de respuestas para que pueda cotejar sus contestaciones con la clave que se publicará en números subsiguientes del Boletín. Se debe obtener una puntuación sobre 70% para obtener crédito.

3. Llenar la hoja de registro y enviarla antes de la fecha que se especifica en la misma. La hoja debe ser enviada con un cheque o giro a favor de la Asociación Médica de Puerto Rico a la siguiente dirección: *Asociación Médica de Puerto Rico, Instituto de Educación Médica, Apartado 9387, Santurce, Puerto Rico 00908.*

Basal and Squamous Cell Carcinomas of the Skin March 1989

Answers

1. False
2. True
3. True
4. True
5. False
6. True
7. True
8. True
9. True
10. True



Hoja de Inscripción EMC



Circular la Contestación Correcta

1. a, b, c, d, e
2. a, b, c, d, e
3. a, b, c, d, e
4. a, b, c, d, e
5. C, F
6. C, F
7. C, F
8. C, F
9. C, F
10. C, F

BOLETIN ASOCIACION MEDICA DE PUERTO RICO

Acute Appendicitis
May 1989

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Life is just too wonderful to give up on. And, as I found out, you don't have

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El Comité del Programa Científico invita a enviar resúmenes de ponencias de trabajos originales para considerarse para presentación durante la sesión científica que se efectuará los días 13, 14 y 15 de octubre de 1989.

PARA MAS INFORMACION ESCRIBA O LLAME A:



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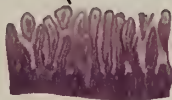
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Fecha límite para entregar los trabajos: 31 de mayo de 1989



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BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:

1. Eliakim R, Ophir M, Rachmilewitz D. *J Clin Gastroenterol* 1987;9(4):395-399.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

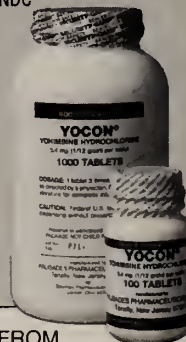
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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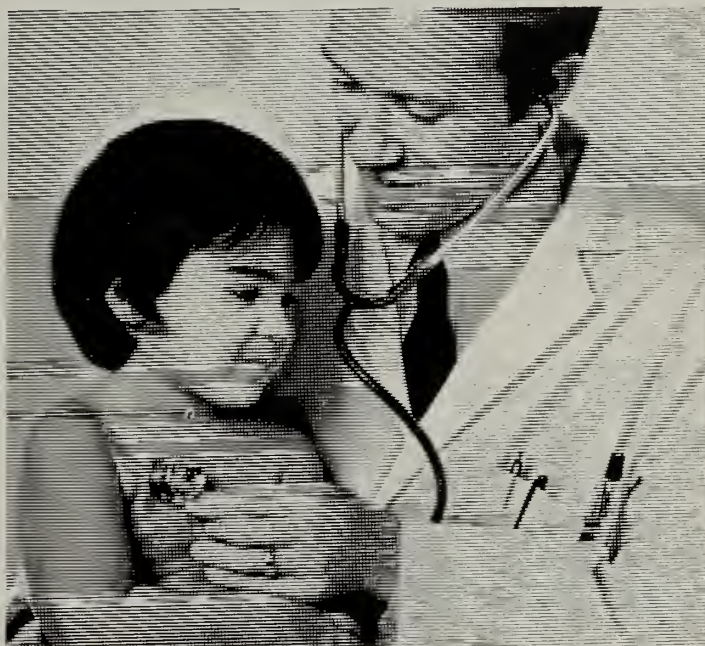
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ESTUDIOS EXPERIMENTALES

Efectos de la Extirpación del Area Piriforme sobre la Ultraestructura de la Corteza Suprarrenal

Alfonso López-Muñiz, MD
Jacinto De Miguel, MD
Isabel Esteban León, MD
Alfonso López Alba, MD
Esperanza Bengoechea, MD
Antonio Pérez-Casas, MD

Resumen: Hemos estudiado la ultraestructura de la corteza suprarrenal de 40 ratas macho Wistar, de pesos entre 200 y 250 gm.

Los animales fueron divididos en 3 grupos: grupo control (animales intactos o animales de operación simulada); grupo experimental I (animales sacrificados al mes de la operación) y grupo experimental II (animales sacrificados a los dos meses de la operación).

Los animales experimentales fueron sometidos a la extirpación bilateral del área piriforme.

Hemos observado un progresivo decremento de las gotitas lipídicas (y de la esteroidogénesis) y un incremento de las alteraciones mitocondriales en las células de la capa fasciculada y también en las células de la capa reticular; lo que indica la existencia de una disminución en la elaboración de las hormonas cortico-suprarrenales. Estos hallazgos nos sugieren que el área piriforme estimula la elaboración de hormonas por la corteza suprarrenal.

El sistema nervioso constituye el elemento receptor y procesador de las informaciones que procedente del medio externo e interno llegan hasta él, y envía las órdenes necesarias para el mantenimiento de la homeostasis y la adaptación al medio por los sistemas efectores, siendo uno de los principales el sistema endocrino.¹

Las conexiones entre el sistema nervioso y el sistema endocrino muestran una gran complejidad y no siguen el esquema general de los sistemas efectores, pues los axones terminan a nivel hipotalámico sin abandonar el sistema nervioso central (no abordando el órgano endocrino efector) y la vinculación última se establece mediante una cadena de sustancias secretadas y de conexiones vasculares cuyo elemento fundamental es la

glándula hipofisaria.^{2, 3, 4}

Este eje hipotálamo-hipofisario se halla, a su vez, influenciado por una estructura más elevada del sistema nervioso central; el sistema límbico. Este constituye un complejo conjunto de estructuras nerviosas que ejercen influencias facilitadoras o inhibitoras sobre el sistema endocrino, además de su papel fundamental y estrechamente imbricado con el anterior sobre los aspectos institivos y emocionales del individuo. A su nivel, y conjuntamente con los otros dos sistemas analizadores-integradores de la hipótesis de Herrick,⁵ la formación reticular y el sistema tálamo-cortical, se elaboran las respuestas más idóneas para el mantenimiento del individuo y de la especie.⁶

La corteza suprarrenal, de origen mesodérmico (a diferencia de la médula suprarrenal con origen ectodérmico y perteneciente al complejo sistema APUD) constituye un importante órgano endocrino, pues su integridad es indispensable para la vida; presentando una estructuración en tres capas: glomerular, fascicular y reticular, que secretan respectivamente aldosterona, cortisol y andrógenos.⁷⁻⁸

La aldosterona se rige por un sistema relativamente independiente (sistema renina-angiotensina-aldosterona) y los andrógenos son secretados en pequeñas cantidades y sólo adquieren una importancia clínica cuando existe un aumento exagerado de su producción. El cortisol es el principal producto elaborado por la corteza suprarrenal y el control de su producción así como el mantenimiento de la estructura, crecimiento y función de la corteza, están regulados por la hormona adenohipofisaria ACTH, siendo su existencia imprescindible para la glándula, influenciando incluso la secreción de otras hormonas no directamente relacionadas con ella (los mineralcorticoides y los esteroides sexuales).⁹

La ACTH está controlada por el CRF, secretado a nivel hipotalámico, y cuya producción es inducida por la llegada de estímulos corticales ante circunstancias especiales, además de seguir basalmente un ritmo circadiano.

Material y Métodos

Hemos empleado 40 ratas macho, cepa Wistar, de edades comprendidas entre 8 y 10 semanas, y pesos entre 200 y 250 gm.

Todos los animales, controles y experimentales, fueron sometidos a las mismas condiciones ambientales (luminosidad, temperatura, humedad...) y alimentación con agua potable "*ad libitum*", y pienso específico para ratas y ratones.

Los animales fueron clasificados en tres grupos:

1. Animales controles, formado por los animales intactos (10) y los animales sometidos a operación simulada (10).
2. Animales experimentales sometidos a la extirpación del área piriforme del lóbulo temporal, y sacrificados al mes de la intervención: Experimental Grupo I (10).
3. Animales sometidos a la extirpación de la región piriforme del lóbulo temporal y sacrificados a los dos meses de ser intervenidos: Experimental Grupo II.¹⁰

Método Experimental

Los animales son anestesiados con pentobarbital sódico, 40 mg/kg de peso. Se procede a la fijación del animal en un marco semejante a los empleados en los aparatos de estereotaxia, diseñado en nuestro departamento.

Se procede al marcado y desinfección del campo operatorio. Se realiza una incisión en forma de V. Se despegua la aponeurosis epicraneal y se desinserta el borde superior del músculo temporal.

Se practica una craniotomía con un trépano cilíndrico por debajo del arco cigomático.

Se accede al cerebro por debajo de la *incisura rhinalis* que se toma como límite superior de la resección. El límite anterior de la exéresis será el borde posterior de la fosa craneal anterior y el límite posterior coincidirá con la fosa temporal. El límite medial se localiza 6-8 mm con relación al límite lateral.

Se eliminan los restos de tejido por aspiración y tras la hemostasia se sutura por planos.

La duración media de la intervención es 40 a 50 minutos.

Se someten los animales a vigilancia y cuidados posoperatorios.

Técnica de la Microscopia Electrónica

Tras ser anestesiados, todos los animales son perfundidos en el ventrículo izquierdo usando una serie estandar de soluciones intravenosas. La perfusión se realiza a una presión aproximada de 100 mm Hg.

Se emplea una solución salina previa (solución normal con 1 cc de heparina sódica por 100 ml) para la vasodilatación del sistema circulatorio hasta obtener un retorno limpio en la aurícula derecha. Inmediatamente se perfunde glutaraldehído al 2.5% en buffer fosfato (ph 7.4)

Las piezas se tallan en bloques de 1 mm y son posfijadas en una mezcla de glutaraldehído al 2.5% en buffer fosfato (ph 7.4) durante 1 hora a 4 grados. A continuación se tratan en otra solución tamponada a 4 grados durante 12 horas, y finalmente con una solución de

tetróxido de osmio tamponado en fosfato a ph 7.4 durante 2 horas.

Los tejidos son deshidratados en una serie de alcoholes etílicos de graduación creciente, aclarados con óxido de propileno, y embebidos en EPON.

Posteriormente se realizan cortes ultrafinos a 50 nm.

Las secciones fueron coloreadas con acetato de uranilo y citrato de plomo y examinadas con un microscopio electrónico Zeiss EM9A.

Se realizan cortes semifinos del cerebro para estudiar el área piriforme y comprobar que la intervención ha sido correcta.

Resultados

Control

La *capa glomerular* presenta su estructura típica, con una densa matriz colágena, donde se encuentran pequeñas células de núcleo grande e irregular, frecuentemente arqueadas, y con nucleolo; y de escaso citoplasma en el que destacan sáculos endoplasmáticos con abundantes ribosomas (Fig. 1A-1B).

La *capa fasciculada* que constituye la mayor parte de la corteza, está formada por columnas de células grandes de

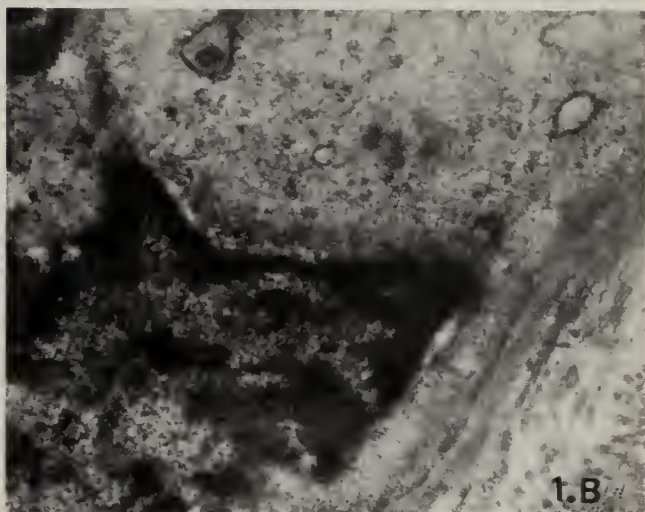
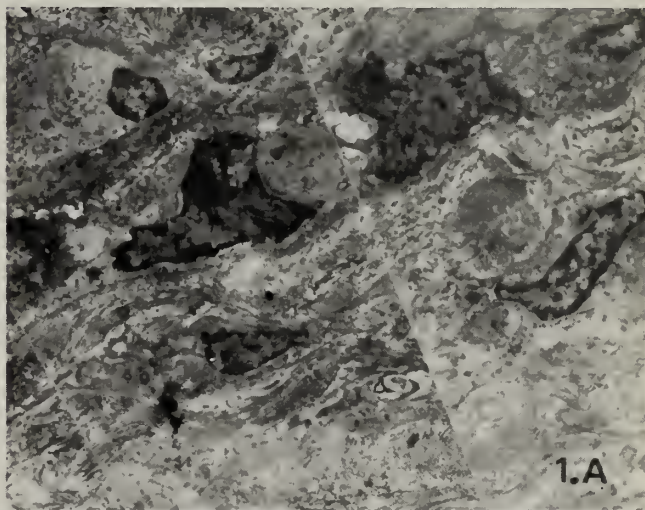


Figura 1.-B Animal Control. Capa glomerular. 1A:6.870X 1B:34.350X

núcleo central, regular, redondeadas y generalmente con nucleolo; su citoplasma contiene abundantes mitocondrias redondeadas, ricas en crestas tubulares irregularmente distribuidas, membranas constituyentes de r.e.r. (frecuentemente se demuestran ribosomas libres) y gran número de vacuolas lipídicas relacionadas con la esteroidogénesis (Fig. 2A-2B).

La *capa reticular* está formada por células semejantes a las anteriores, aunque su núcleo es más irregular y de cromatina más densa. En los citoplasmas destacan abundantes mitocondrias con numerosas crestas tubulares, grandes vacuolas lipídicas, y condensaciones pigmentarias (Fig. 3A-3B).

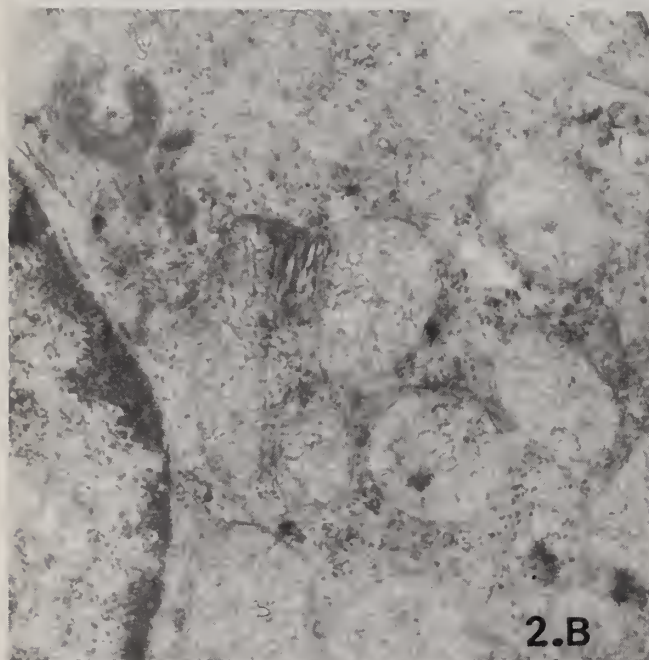
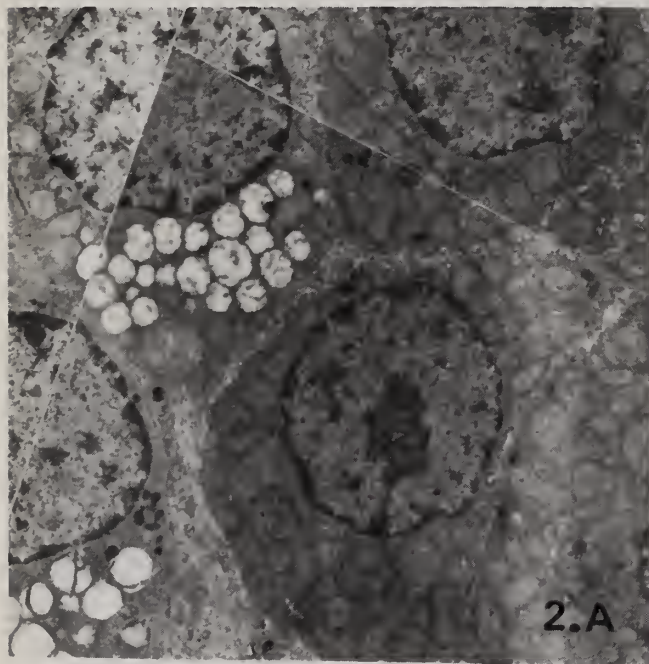


Figura 2.-B Animal Control. Capa fasciculada. 2A:6.870X 2B:34.350X

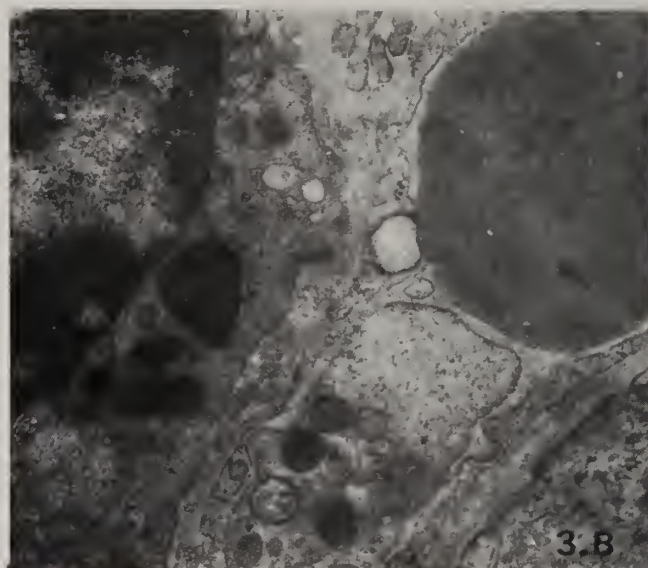
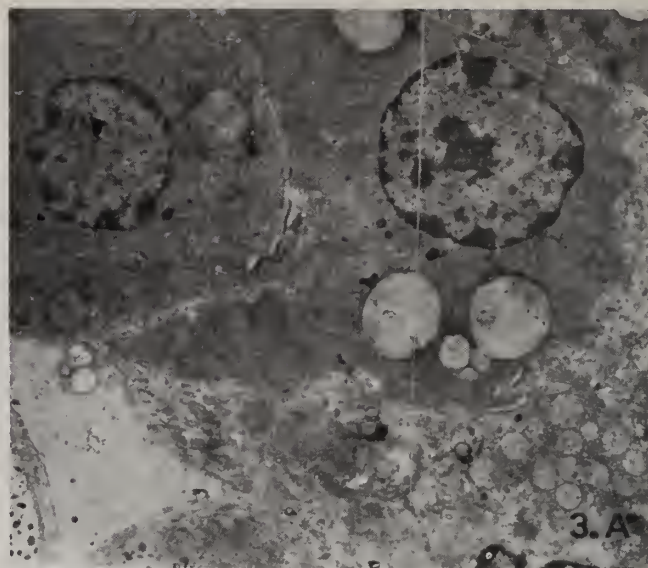


Figura 3.-B Animal Control. Capa reticular. 3A:6.870X 3B:34.350X

Experimental Grupo I

En la *capa glomerular* no se observa ninguna modificación significativa (Fig. 4A-4B).

Las células de la *capa fasciculada* poseen un núcleo de características normales, con la cromatina en la proximidad de la carioteca y la existencia constante de nucleolo. En los citoplasmas se demuestra la abundancia de mitocondrias (que conservan sus crestas tubulares), ligera disminución de las vacuolas lipídicas y la aparición de lisosomas secundarios (Fig. 5A-5B).

En la *capa reticular* las células poseen escasas diferencias con las descritas en los animales controles, destacando un ligero decremento de las vacuolas lipídicas, y la existencia de mitocondrias alteradas (con sus crestas desestructuradas) y de fagolisosomas (Fig. 6A-6B).

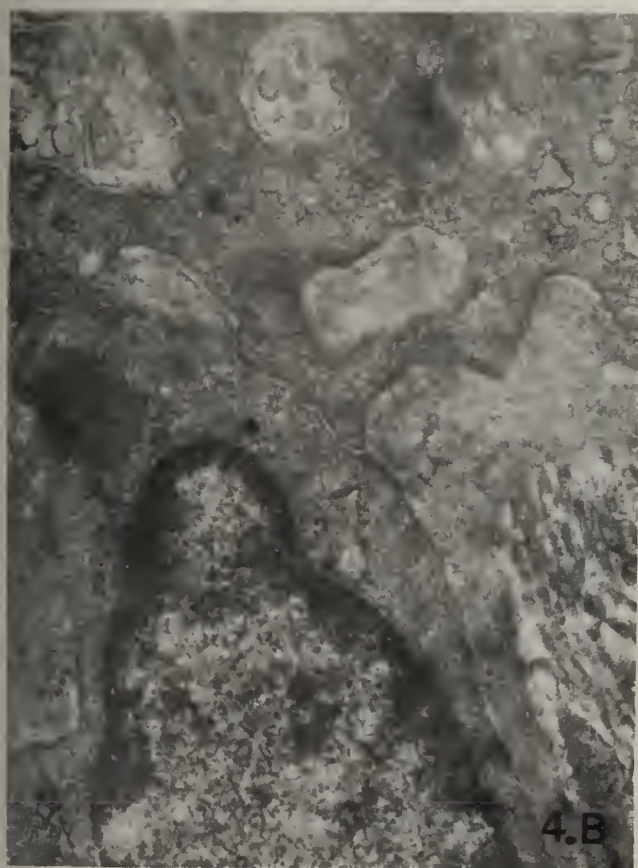
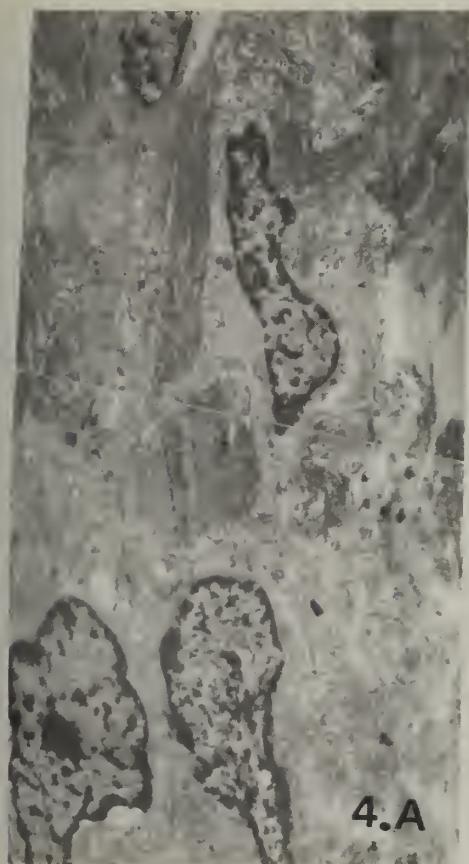


Figura 4.-B Animal EXPERIMENTAL I. Capa glomerular. 4A:6.870X
4B:34.350X

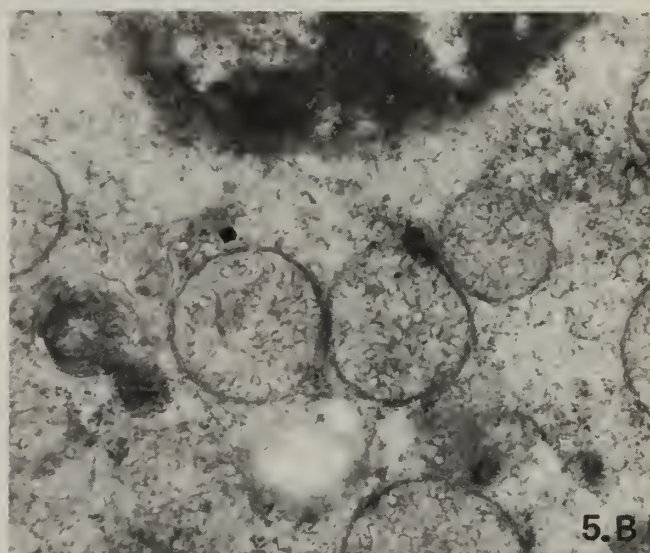
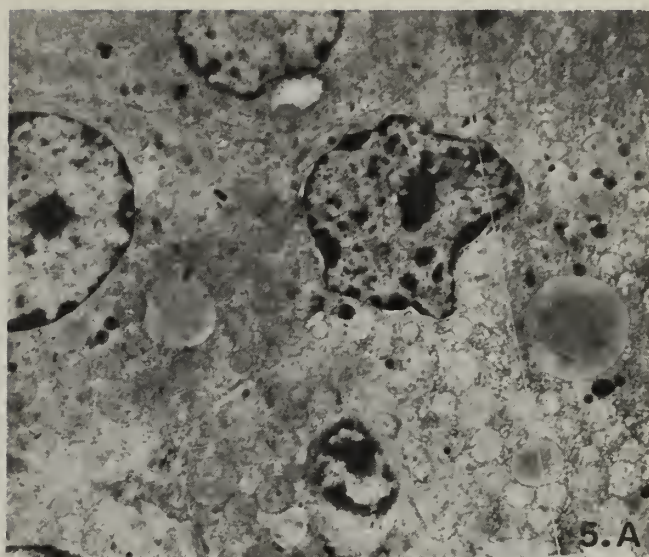
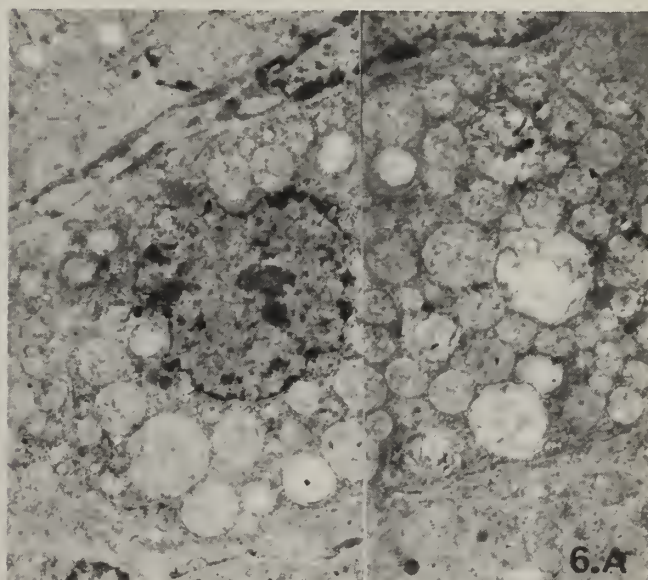


Figura 5.-B Animal EXPERIMENTAL I. Capa fasciculada. 5A:6.870X 5
B:34.350X



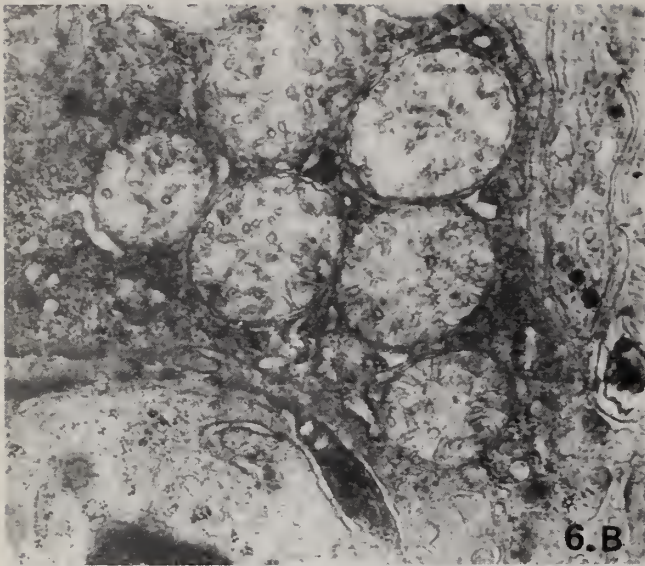


Figura 6.-B Animal EXPERIMENTAL I. Capa reticular. 6A:6.870X
6B:34.350X

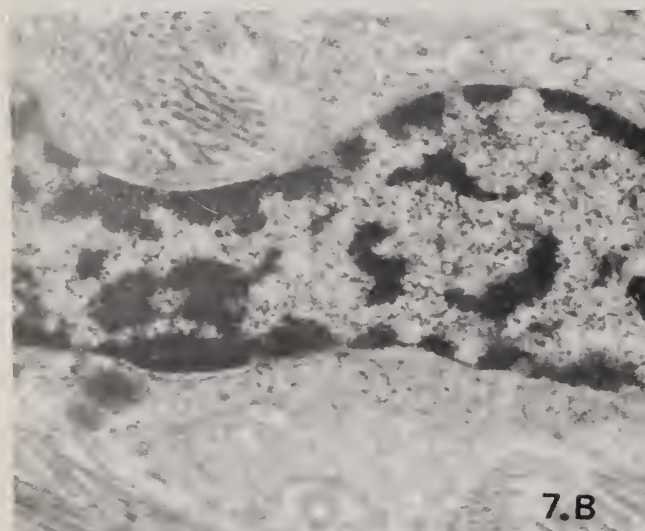
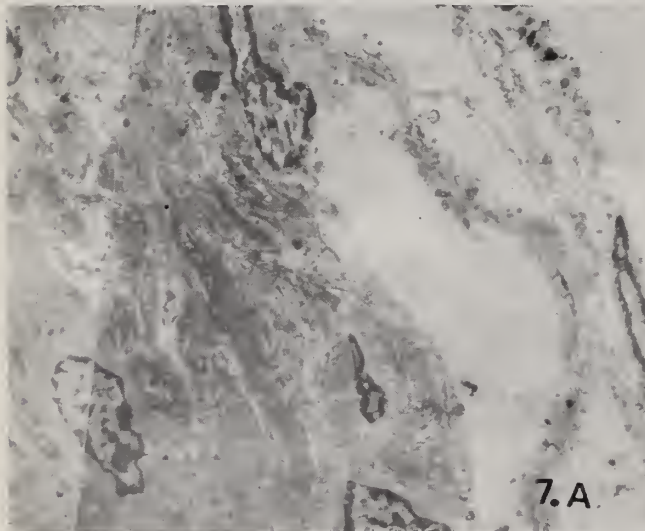
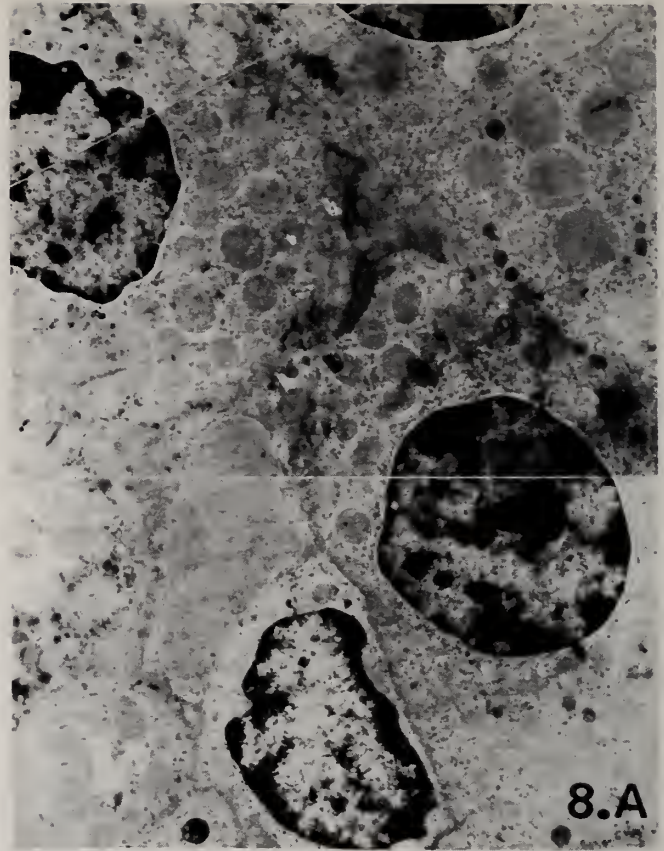


Figura 7.-B Animal EXPERIMENTAL II. Capa glomerular. 7A:6.870X
7B:34.350X

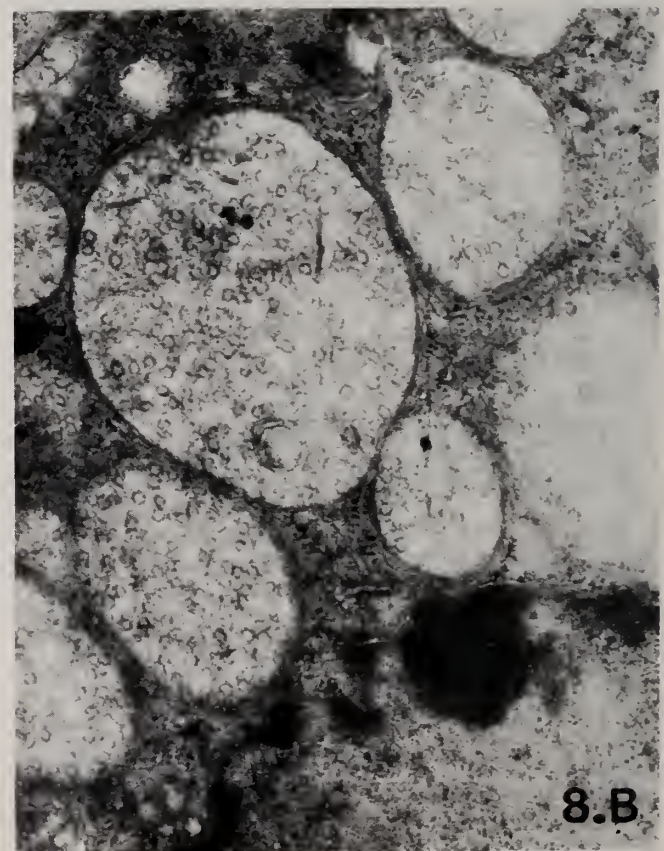


Figura 8.-B Animal EXPERIMENTAL II. Capa fasciculada. 8A:6.870X
8B:34.350X

Experimental Grupo II

La corteza suprarrenal presenta modificaciones más significativas que en el anterior experimento.

En la *capa glomerular* existe un ligero descenso de la celularidad (Fig. 7A-7B).

Parece existir un ligero aumento de la colágena en la *capa fasciculada*. Las células presentan en su citoplasma una disminución del número de vacuolas lipídicas y alteraciones mitocondriales (donde las crestas pierden su estructura tubular) (Fig. 8A-8B).

En las células de la *capa reticular* se demuestran alteraciones nucleares y en los citoplasmas una acentuada disminución del número de vesículas lipídicas, con la aparición de otras de gran diámetro, que llegan a comprimir al núcleo, y numerosos fagolisosomas (Fig. 9A-9B).

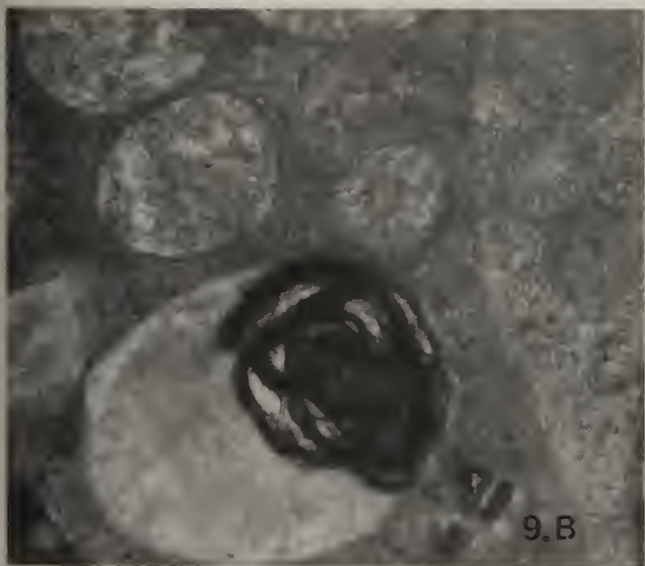
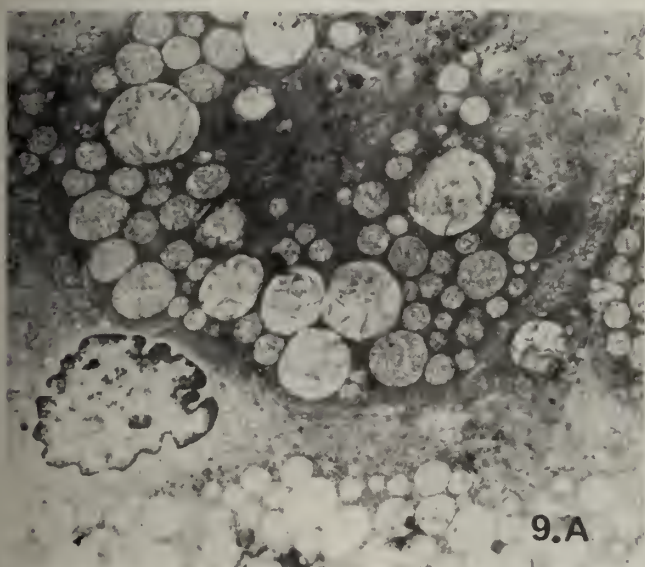


Figura 9.-B Animal EXPERIMENTAL II. Capa reticular. 9A:6.870X
9B:34.350X

Discusión

El estudio de la relación existente entre el sistema límbico y la glándula suprarrenal representa una ardua labor debido a la complejidad estructural y la dificultad de estimular o destruir selectivamente determinadas áreas límbicas, sin afectar estructuras adyacentes. Sin embargo existe una amplia serie de estudios que analizan este tema.^{10, 11, 12}

La amígdala constituye el más importante complejo nuclear del sistema límbico, su estimulación provocaría una acusada respuesta corticosuprarrenal según algunos autores, aunque no está aclarado la participación en condiciones basales de los distintos subnucleos que la forman.^{13, 14, 15, 16, 17}

El hipocampo es la principal estructura cortical límbica; su estimulación da lugar a una disminución de la secreción de ACTH^{13, 14, 15} posiblemente por inhibir la función de la amígdala cerebral.

El neocortex ejerce genericamente sobre la amígdala una función inhibitoria.¹⁸

Mientras que algunos investigadores encuentran que la estimulación del hipotálamo posterior produce una disminución en la liberación de ACTH,^{19, 20, 21} otros autores afirman que esta disminución se vería precedida por un aumento inicial de la secreción corticoadrenal.²²

La estimulación química (adrenérgica o colinérgica) de la banda diagonal de Broca, el área septal media, la región preóptica y el preosencéfalo, origina un descenso en la secreción adrenocortical.²³

En nuestro estudio hemos encontrado un progresivo descenso de las vacuolas lipídicas (lo que debe relacionarse con un decremento de la esteroidogénesis), y un incremento de las alteraciones en las crestas mitocondriales (que demuestra la existencia de una grave afectación de las rutas energéticas).

En conjunto hemos observado que las células de la capa fasciculada, así como las células de la capa reticular, presentan profundas modificaciones histofuncionales, que traducen una disminución en la elaboración de hormonas suprarrenales fundamentalmente glucocorticoides.

Estos hallazgos coinciden con los descritos en la bibliografía en relación con la amígdala, ya que la estimulación del complejo nuclear amigdalino lleva a un aumento en la función de la corteza suprarrenal; mientras que el hipocampo tendría la función opuesta.

Summary: We have performed a study about the ultrastructure of the suprarenal cortex in 40 male Wistar rats whose weights oscillated between 200 and 250 grammes.

The animals were divided in three groups: control group (untouched animals or with simulated operation); experimental group I (animals sacrificed a month after the operation); and experimental group II (animals sacrificed two months after the operation).

In the experimental animals, we have performed the bilateral extirpation of the piriform area.

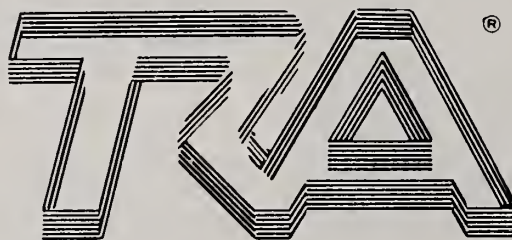
We have found a progressive decrease of the lipidic droplets (and of the steroidogenesis) and an increase in the mitochondrial alterations in the cells of fasciculate layer,

and also in the cells of reticular layer; what indicates the existence of a decrease in the elaboration of cortex-suprarenal hormones. These results suggest us that the piriform area stimulates the elaboration of hormones by the suprarenal cortex.

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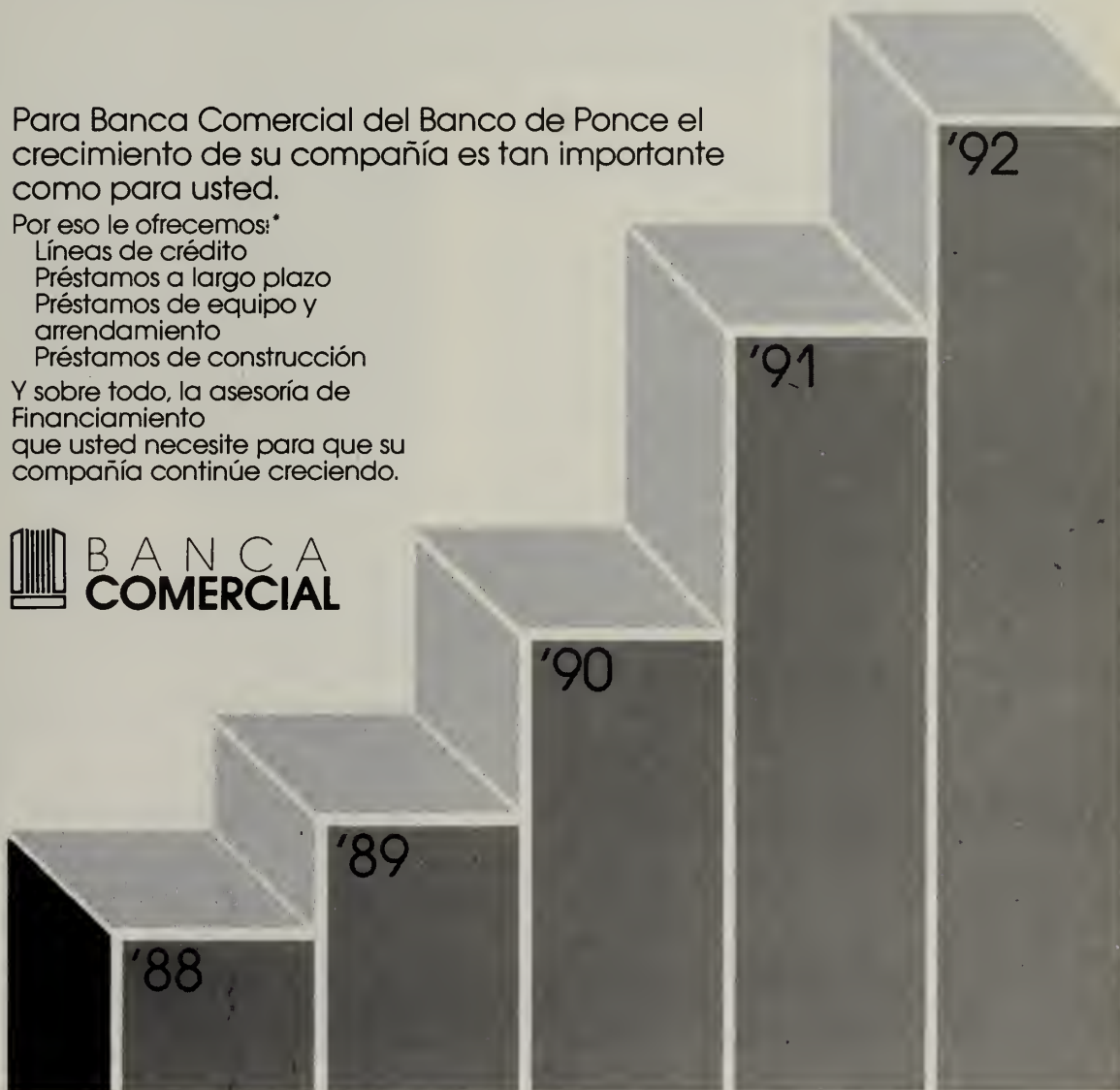
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CASE REPORT

Cholecystitis Due to *Schistosoma Mansoni*, Fact or Fancy

Manuel A. Marcial, MD, FCAP, FACP
Raúl A. Marcial-Rojas, MD, FCAP, FACP

Summary: A case of a 50-year-old female with schistosomiasis of the gallbladder is reported. The clinical and pathological findings are presented.

Schistosomiasis mansoni may occasionally involve the gallbladder producing symptoms that simulate chronic cholecystitis.¹⁻³ In the majority of these cases the serosa contains numerous bilharzial pseudotubercles. The accompanying chronic inflammation and fibrosis result in a fibrous and thickened gallbladder wall. However, the mucosa is rarely affected and intramucosal oviposition is the exception rather than the rule. We report a case of schistosomiasis mansoni of the gallbladder with the presence of numerous eggs in the mucosa and adult forms within a venule in the gallbladder wall.

Report of a Case

A 56-year-old female was referred to our surgery clinic with a two year history of right upper quadrant pain which radiated to the back. The pain was accompanied by nausea and was associated with ingestion of fatty foods. The physical examination was unremarkable except for right upper quadrant tenderness. She had a normal ECG and chest x-ray. Laboratory findings included a hemoglobin of 12.7 gm/dl, alkaline phosphatase of 142 U/L, SGOT of 31 U/L and a bilirubin level of 0.6 mg/dl. Radiologic evaluation of the gallbladder revealed the presence of gallstones.

A cholecystectomy was performed with a preoperative diagnosis of cholelithiasis. The gallbladder specimen measured 10 x 2.5 x 2.0 cms. and the serosal surface was smooth and glistening. The walls were thickened, and the mucosa was velvety and bile-stained. Numerous multifaceted calculi were noted, the largest of which measured 1.8 cms. Microscopic examination revealed evidence of chronic cholecystitis with focal mucosal atrophy, Rokitsansky-Aschoff sinuses and pseudopyloric glandular metaplasia. Numerous *S. mansoni* eggs with living embryos were seen within the mucosa of the gallbladder (Figs. 1 and 2). The characteristic lateral spine was

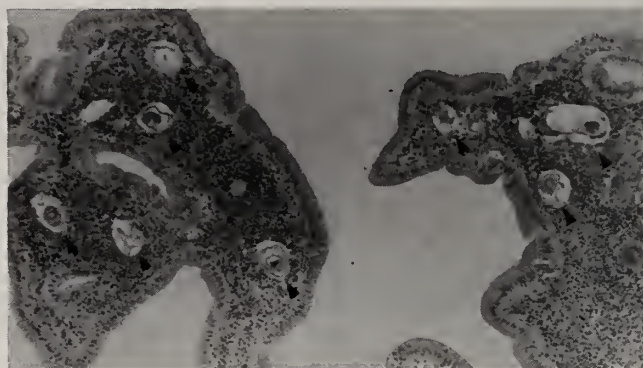


Figure 1. Low power photomicrograph of the gallbladder mucosa revealing multiple *Schistosoma* eggs (arrowheads).

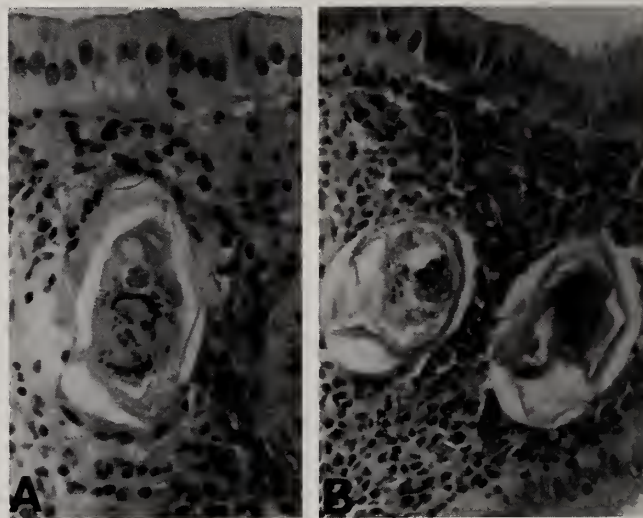


Figure 2A, B. *Schistosoma mansoni* eggs with living embryos within the lamina propria. A prominent inflammatory infiltrate rich in eosinophils is noted (B).

identifiable in several of them. The lamina propria surrounding the eggs was densely populated with inflammatory cells with a marked predominance of eosinophils (Fig. 2). Bilharzial pseudotubercles composed of granulomatous inflammation surrounded the parasitic eggs in the submucosa (Fig. 3).

It is one of the author's (RAMR) experience that when- ever this number of eggs are locally seen, an adult worm is usually found blocking the draining vessels of the area

involved. Thus, multiple additional sections were examined searching for the culprit adult couple. Luckily, in one of the sections the male and female adult worms were found within a venule (Fig. 4).

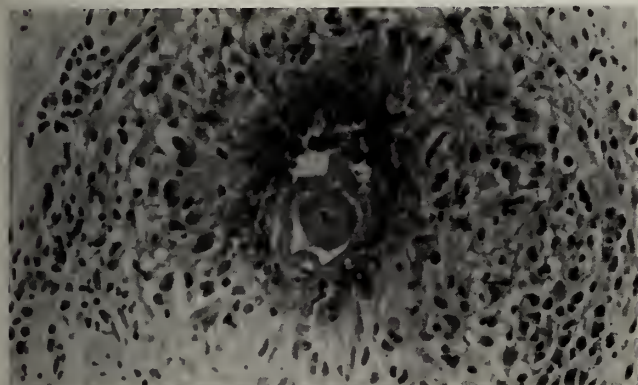


Figure 3. Typical circumoval granuloma with centrally placed egg, mantle of epithelioid histiocytes and outer zone of lymphocytes.

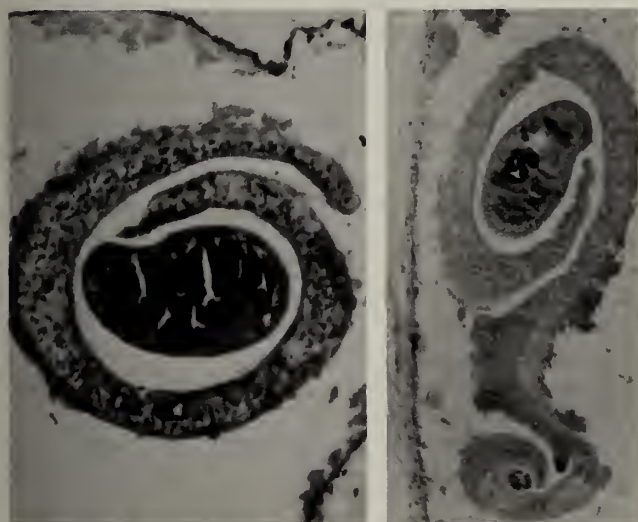


Figure 4. Cross sections of the adult schistosome couple inside a gallbladder venule. The smaller adult female lies within the male gynecophoral canal.

Comment

The etiology of chronic cholecystitis is not well understood. Although chronic cholecystitis is almost always associated with the presence of gallstones, a direct cause and effect relationship has never been unequivocally established. Infection by enteric bacteria is also an unlikely cause, cultures being positive only in a minority of the cases. Most investigators believe that lysolecithin production in supersaturated bile leads to chemical unjury and inflammation of the mucosa. However, this theory is not universally accepted.

That schistosomal infection can lead to mucosal inflammation in such organs as the colon and urinary bladder is a well known fact. In our case, the gallbladder, although infected with schistosoma, also contained gallstones. Thus, a diagnosis of schistosomal cholecys-

titis could not be categorically rendered. However, in the only other case we know of prominent gallbladder bilharzial parasitism, cholelithiasis was not present, and still the patient presented with cholecystitis. Therefore, there is a possibility that, although rare, schistosomal cholecystitis really exists as a nosologic entity.

Resumen: Se informa el caso de una mujer de 56 años de edad con el diagnóstico de Esquistosomiasis de la vesícula biliar. Los hallazgos clínicos y patológicos del caso son presentados en este reporte.

Acknowledgements

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Dilemas de la Práctica de la Medicina para el Siglo XXI

La Etica y El Trasplante de Organos

Eduardo A. Santiago Delpín, MD

Conviene ubicar cualquier sistema ético especializado en el contexto de una ética universal animal. Sí, los animales tienen ética. Sus sistemas de ética no existen dentro de un marco social, sino que son gobernados por la evolución de los rasgos beneficiosos a su especie, la cual, con infinita paciencia, talla en el gen imperativos protectores al individuo y la especie. Con el revolucionario aumento del tamaño del cerebro y el consecuente exponencial desarrollo de códigos sociales —algunos de los cuales son mayores que el código básico informacional— se perdió en parte este código automático de ética.

No obstante, el hombre ha estado consciente de la necesidad de mantener sistemas de comportamiento que permitan la convivencia, desde siempre; lo sabemos desde la palabra escrita. Desde el punto de vista ético son sorprendentemente iguales las enseñanzas de Confucio en sus libros de ética como lo son las que se expresan en la Biblia, en el Bhagavad-Gita del Hinduísmo, en las enseñanzas del Buddha en el Dhammapadam, y el Tao hermosamente transcrito por la Lao Tzu. Amarga ironía es que en el hoy de fines de milenio, los líderes —muchos en realidad son caudillos tribales y nada más— dediquen su tiempo a leer el libro de guerra de Sun Tzu "El arte de la guerra", y no los otros.

El médico curandero desde siempre estuvo consciente de la ética, y el escritor del Papiro de Smith acompaña el detalle técnico de cómo inmovilizar y curar una fractura de hueso, con la consciencia de no hacer daño y de evitar el dolor. Ese gran libro de medicina interna, el Nei Ching, comienza con consejos sabios para el hombre y para el paciente. Los aforismos de Hipócrates nos llegan hasta hoy. Avicenna y el mundo árabe acompañaba su código diagnóstico con un código ético. El Religio Medici de Browne lo mismo. Lo resume Paracelsus aproximadamente en el 1520 en su famoso Credo, que dice en parte: "Esta es mi promesa. Perfeccionar mi arte médico y jamás desviarme de él mientras Dios mantenga mi oficio. Oponer toda medicina y enseñanza falsa. Amar al enfermo, a todos y cada uno de ellos, más que si mi cuerpo fuera el que estuviera enfermo. No juzgar nada superficialmente sino por síntomas, ni administrar

medicamentos sin entenderlos, ni recoger dinero sin ganarlo. *No adivinar, sino saber...*"

Trasplante de Organos

Esta disciplina que hoy nos parece tan natural y que no tiene la connotación de milagro que tuvo en antaño (antaño es hace diez o quince años atrás), comenzó a principios de siglo cuando la ciencia reconoció que habían circunstancias donde tan sólo un órgano estaba irremisiblemente dañado y que su sustitución podía devolver al paciente a la salud. Desde que Carrel perfeccionó la técnica de coser arterias y venas se están haciendo experimentos en trasplante. No menos de 20 publicaciones existen en el campo de la trasplantología experimental entre 1900 y 1950. Los experimentos en humanos comenzaron en Europa en la década de los treinta, pero fue en los cincuenta donde los grupos pioneros de Boston llevaron a cabo los primeros trasplantes con éxito. Habría de esperarse más de cincuenta años en lo que se lograba el primer éxito, producto de la intuición de que el problema no era técnico sino inmunológico. Pero recordemos que en esta época, el sistema inmunológico era un párrafo, y el linfocito, su protagonista principal, algunas líneas en libros de patología clínica y de inmunología. Recordemos que los inmunosupresores, todos venenos metabólicos, estaban recién descubiertos y que no se conocía su acción precisa y sobre todo sus complicaciones. Habían pocas instituciones y centros haciendo estos estudios. No había cubierta económica.

De esta experiencia inicial surgieron, a través de los años, por lo menos cinco áreas con planteamientos éticos de importancia.

Los Experimentos Iniciales en Diálisis y Trasplante

En esa época inicial no se sabía casi nada del efecto de un rodillo, un tubo de goma, y de una membrana de celofán en los elementos formados y en las proteínas de la sangre. ¿Cuál membrana? ¿Cuánto dialisar? ¿En qué paciente? ¿Cuántas veces y por cuánto tiempo? ¿Por cuál vía? La mortalidad era alta. La experiencia poca.

En el área de trasplante se usaron los esteroides porque eran anti-inflamatorios y las biopsias de los órganos rechazados demostraban una gran cantidad de "inflamación". Los venenos metabólicos como la azatioprina, cogieron auge porque los hematólogos nos dijeron que

había hiperplasia celular y ya se sabía que estas células eran susceptibles a la acción de ellos. La administración se aprendió sobre la marcha, con poca experimentación animal. La mortalidad por las complicaciones era altísima.

En otras palabras, se desarrolló esta temprana fase del trasplante y la diálisis *sin saber*. ¿Es esto un planteamiento ético? Lo es sin duda. Hoy miramos hacia atrás con el conocimiento de los medicamentos y de la tecnología, pero en aquel momento los practicantes de esta disciplina estuvieron profundamente sumidos en la posición agobiante de una terapia desconocida y trunca, que tenía alta mortalidad. ¿Qué lo redimió? El hecho de que prolongaban la vida, mitigaban el dolor, y permitían una supervivencia mayor —aún cuando fuera un porcentaje pequeño— sobre la enfermedad inicial. Esta observación se puede considerar como un principio en los planteamientos éticos, junto con añadir una intención buena y un investigador honrado.

El Uso de Donantes Vivos

Todos los programas de trasplante del mundo consideran la donación *de vivo* como una de las acciones más excelsas de que es capaz el ser humano. En reconocimiento al altruismo, se desvive el practicante de trasplante en estudiar a este donante de la manera más minuciosa posible, de manera que llegue al momento de la donación en perfecta salud y perfecta condición para donar. Si no está perfectamente saludable se viola un principio fundamental y se cae en una práctica que no es ética. En muchas de las situaciones donde ha habido complicaciones en donantes, esto ha ocurrido porque se ha alterado en algún momento la perfección del proceso, circunvinando algunas de las salvaguardas.

Otro problema. Un trasplante usando *donante vivo* tiene mejores resultados que uno usando cadáver. Se pregunta uno si en las discusiones con el donante vivo hay algún tipo de coerción inconsciente hacia los posibles familiares que donen. ¿Cuánto es descripción objetiva de la verdad y cuánto es coerción? ¿Estamos modificando su motivación? Este es un planteamiento diario en los programas de trasplante y el traerlo a la consciencia permite hacer las presentaciones al donante lo más objetivamente posible.

¿Los niños? La inclinación natural es no usar niños bajo ninguna circunstancia. No obstante, el hecho de que algunos jóvenes menores de edad tengan ya la capacidad y el conocimiento suficiente para entender lo que le ocurriría al familiar enfermo si ellos no donan, obliga a mirar con detalle este problema ético. En muchos lugares, incluyendo Puerto Rico, se ha abordado el problema de la siguiente manera. Un donante menor de edad (ciertamente no menor de 15 años, aunque esto es arbitrario) debe entender cuál es el problema envuelto; debe comprender la magnitud del riesgo; debe tener la capacidad para decidir; estará en perfecta salud; sufriría daño de no permitírsele donar. Finalmente, los Tribunales de Justicia asignarán un tutor para quitar la responsabilidad de esta magna decisión a los padres. La otra alternativa es que la persona esté emancipada legalmente en cuyo caso la Corte identifica esto con la capacidad de decidir.

Otro planteamiento sobre donación, coerción, soborno y chantaje ocurre al utilizar una población de *presidarios*. Esta práctica ya no existe.

El *donador vivo no familiar* está siendo usado con mayor frecuencia. Si se contempla aceptar la donación de una esposa o un amigo, es preciso el escrutinio intenso de la motivación de esta persona y la ausencia de cualquier otra transacción comercial que sugiera compraventa de órganos. En presencia de matrimonios o amistades estables es permisible la donación, siempre y cuando se cumplan los mismos requisitos que se aplican a los niños.

Compraventa de órganos. Nuestra primera reacción es negativa porque al entrar en una relación de compraventa ocurren posibilidades de soborno antes del trasplante, y chantaje después del trasplante. Además, dada la carestía de órganos, inmediatamente surgiría un mercado negro con leyes de comercio controlando la disposición de órganos. Sin embargo, en la India se practica la compraventa de órganos: el órgano lo paga el paciente pudiente a una persona usualmente muy pobre. Argumentan los que defienden esta práctica que de esta manera la persona recibe su órgano y una familia recibe sustento para una familia entera para toda la vida. Por supuesto, se trasplanta sólo el que puede pagar.

El Donante Cadavérico

En su día el uso del órgano cadavérico generó planteamientos éticos de gran magnitud. Por ejemplo, la *definición de muerte*. Tomó casi veinte años el cobrar consciencia de que tan muerte es el cese total de las funciones cardiorespiratorias, como lo es el cese total e irreversible de las funciones cerebrales incluyendo el tallo cerebral. La muerte cortical es sólo coma. Tiene que incluir la muerte de los centros que gobiernan respiración, corazón y algunas transacciones endocrinas para que ocurra muerte de verdad. Hoy es una cosa automática que aparece en todos los códigos civiles de todos los países del mundo.

¿De quién es el cuerpo? Con la aplicación de leyes universales de donación en prácticamente todos los países, ha surgido el concepto de que el individuo es dueño de su propio cuerpo y puede disponer de él como de cualquier otra propiedad para después de su muerte. De ahí la donación en vida que es un concepto aceptado hoy por la mayor parte de las personas y países.

¿Qué se hace con la persona en *coma*? El tallo no está muerto, sin embargo, esta persona existe tan sólo de una manera vegetativa sin función cortical y cuesta mucho al estado. No quisiéramos pensar en esto como un "issue" ético, pero se está trayendo al foro de discusión internacional.

¿El *anencefálico*? Destinado al cese cardiorespiratorio horas o días después de nacer, este cuerpo no tiene muerte cerebral en el sentido tradicional pero no tiene oportunidad de vida. Ese "issue" está siendo discutido, aunque la reacción actual es en contra de su uso.

El Costo del Trasplante

Queremos pensar que no hay problemas de *costo* en las naciones industrializadas con grandes recursos. No obstante, sí los hay. El aumento de la prestación de servi-

cios renales ha sido mucho mayor y más rápido que el aumento ya de por sí exponencial de los costos del programa de Medicare. Así que, aún en un país rico, tiene un impacto serio la prestación de servicios terciarios. ¿Por esto, se deben interrumpir? No, dice el Norteamericano. Sí, dice el Inglés. En Inglaterra, los servicios de diálisis y trasplante ocurren en el sector privado.

Trasplante y Diálisis. Hay países donde el problema principal es de nutrición, hambre, enfermedades infecciosas, parásitos. ¿Debe este país desarrollar programas de servicios terciarios? Nuestra respuesta inicial es no. No obstante, en la mayor parte de los países donde se ha comenzado esta práctica, a pesar de no existir los recursos que existen en países industrializados, se ha visto aumento y mejoría en todos los parámetros de prestación de servicios de este país. En otras palabras, el desarrollar servicios terciarios resulta en mejoría de otros servicios, y se mejora la medicina completa en este país.

Cuando los Recursos son Escasos

En la década de 1960, cuando había muy pocas máquinas de diálisis en los Estados Unidos, se constituían comités llamados "Comités de Vida y Muerte", que

tenían que decidir a quién se iba a dializar en la única máquina. ¿Debió ser el gobernante que dirige los destinos del país? ¿O el industrial con mucho dinero? ¿Por qué no el padre de familia, un labriego con tres hijos que dependen de él? ¿Por qué no el clérigo cuya grei depende de él para el sustento espiritual? Esta agonía decisional se sigue viviendo hoy cuando los programas de trasplante se confrontan con un sólo riñón cadavérico para muchos posibles recipientes. ¿Cómo se decide a quién dárselo? Hemos desarrollado guías que incluyen compatibilidad, tiempo, estabilidad, edad. Pero los criterios son incompletos, y a veces, después de larga consideración y discusiones, son otros factores o detalles los que inclinan la balanza en una u otra dirección.

Conclusión

Casi todos los practicantes de trasplantes de órganos del mundo se sienten tocados por el milagro del trasplante. Han vivido una vida completa por estar en un área de vanguardia clínica y de investigación, y por ser testigo y partícipe del altruismo del donante y su familia. El precio es la preocupación agobiante y constante por los planteamientos éticos que se suscitan en esta práctica.

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BRIEF SUMMARY CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacological studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment,

may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) have been observed in angina trials. In many cases, the relation to drug uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, lightheadedness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dyspepsia, mild elevations of SGOT, S and LDH (see hepatic warnings), vomiting, weight increase.

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturnal osteoarthritis pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued

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El Fenómeno Urémico y El Fenómeno Encefalopático Hipertensivo en las Nefritis y en la Hipertensión Esencial*

A. Fernós Isern, MD

El fenómeno urémico puede sobrevenir a consecuencia de la obstrucción de la eliminación urinaria por bajo del nivel del riñón; puede ocurrir en casos de riñón deficiente, pero todavía compensante, si se acompaña de deshidratación excesiva por emesis repetida; puede ocurrir, en casos de oliguria por insuficiencia circulatoria sobrepuesta a una deficiencia que no llega todavía a la insuficiencia renal. En estos tres casos la retención urémica no se debe pues a insuficiencia total en la función renal sino a mera deficiencia con otro factor extrínseco sobreañadido. En tales casos el peso específico de la orina puede ser considerablemente superior a 1.010. Si la obstrucción, la deshidratación o la insuficiencia circulatoria el riñón hubiera podido mantener una eliminación suficiente aún cuando en dos últimos casos ello fuera merced a una poliuria compensatoria. *Si el riñón concentra a más de 1.020 es muy difícil concebir la uremia.*

Las lesiones renales per se sólo producen uremia cuando la deficiencia renal llega a tal grado que deviene insuficiencia. Es el fracaso renal, el "renal failure" análogo al "heart failure" o sea a la decompensación, si se quiere usar esta expresión.

Una orina de gravedad específica máxima de 1.010 significa insuficiencia total de concentración y por ende de excreción salvo cuando sobreviene por exceso de eliminación de líquidos como en la resolución de edemas. Mayor de 1.010 revela un riñón capaz de eliminar sólidos en razón directa a la elevación del peso específico y a la cantidad de orina eliminada.

Cuando el riñón resulta incapaz de concentrar a 1.020 el aumento en la cantidad de líquidos eliminados debe compensar la falta de concentración para asegurar la adecuada eliminación de sólidos. Es la poliuria compensatoria análoga a la hipertrofia cardíaca compensatoria. Con gravedad específica a 1.010 o cuando más 1.012 sobreviene la uremia irremediablemente; la poliuria no puede ya compensar. Si sobreviene además el desfallecimiento del miocardio y el embarazo circulatorio, el estado urémico se agrava considerablemente.

La uremia viene acompañada de azotemia, pero la azo-

temia per se no causa uremia; meramente la indica. En la insuficiencia circulatoria sobreviene la azotemia; pero, si no está reducida la capacidad de concentración del riñón, si el funcionamiento del riñón es adecuado, al sobrevenir la oliguria no sobreviene la uremia, pues la concentración urinaria sube proporcionalmente; y en poca cantidad de orina se elimina gran cantidad de sólidos. En tales casos hay azotemia con oliguria y alto peso específico de la orina.

Sentadas estas bases diremos que la uremia es una intoxicación del organismo producida por la insuficiencia renal, por el fracaso del riñón en su labor excretoria. Queda evidenciada la insuficiencia por la incapacidad del riñón para concentrar orina a una gravedad específica bastante mayor que la gravedad específica de la sangre que es alrededor de 1.010. Va acompañada además de un aumento en las sustancias nitrogenadas no proteicas de la sangre, pero no se puede decir que es causada por éstas. Una concentración máxima intermedia y fija entre 1.020 y 1.010 señala riñón deficiente. A medida que se acerca a 1.010 va siendo más insuficiente hasta llegar al "renal failure" de 1.010 o cifras inmediatas, como 1.012. No se puede asegurar qué sustancias retenidas producen la uremia. El concepto actual es que la uremia obedece a la suma de sustancias varias retenidas y no a una sola en particular. La urea puede aumentarse considerablemente en la sangre sin producir síntomas. Su mero aumento en la sangre no produce uremia.

Causalidad de la Uremia

Las condiciones renales que con mayor frecuencia producen insuficiencia de este órgano y por ende uremia son:

1. Nefritis aguda.
2. Glomerulonefritis crónica.
3. Nefroesclerosis.
4. Nefrosis necrótica.

El riñón policístico y la tuberculosis renal son causas menos frecuentes.

Glomerulonefritis Aguda

Es bien conocido el cuadro y el curso de la nefritis aguda con sus síntomas de náusea, y vómitos, diarrea a

veces, oliguria, hematuria, albuminuria, cilindruria, hipertensión, edema, a veces fiebre: pero conviene aclarar su diferenciación de las nefritis focales y las nefritis embólicas.

A diferencia de la glomerular aguda o crónica que tienen una etiología alérgica o cuando menos a base de la acción tóxica de focos microbianos distantes y que sobreviene tras una enfermedad aguda, más comunmente estreptococcica, la nefritis focal obedece al alojamiento en el parénquima renal de focos microbianos de acción localizada o bien a envenenamientos con arsénicos o cantáridas. Salvo que su extensión fuera exagerada, no llega a reducir la suficiencia excretoria renal siquiera venga acompañada de hematuria, cilindruria, albuminuria, piuria y reacción sistémica febril. Tampoco viene acompañada de edema ni de hipertensión, de azotemia o de uremia, ni de retinopatías. En general, consecuencia y concomitante con localizaciones sépticas en las amígdalas u otros posibles focos locales: de neumonías, tifoideas, erisipelas, malaria. La nefritis embólica por otra parte, acompañada de hematuria, albuminuria y cilindruria es por lo general consecuencia de desprendimientos embólicos en la endocarditis u otros fenómenos análogos, que se alojan o destruyen los vasos renales. Pero sus síntomas generalmente no pasan de ahí.

Glomerulonefritis Crónica

La glomerulonefritis crónica es un proceso inflamatorio crónico que bien se desarrolla insidiosamente como continuación de un proceso de glomerulonefritis agudo originalmente inadvertido o bien es la clara continuación de un franco proceso agudo que pasa al estado subagudo y al fin crónico, o calladamente al crónico. Una gradual destrucción del tejido funcional del riñón de lugar a la formación progresiva de tejido cicatricial inactivo. El número de unidades renales en función va paulatinamente disminuyendo. Siendo el número de aquellas tan extenso y por tanto tan grande la reserva de la capacidad renal, queda explicada la lentitud con que se llega al punto en que el número de unidades en función es insuficiente para las necesidades excretorias del organismo, para que se manifieste la insuficiencia renal con sus secuelas y sobrevenga la más grave, la uremia.

A diferencia de la glomerulonefritis aguda termina en la muerte durante el ataque o bien evoluciona hacia la forma subaguda y crónica. La glomerulonefritis crónica una vez establecida, durante su primer año de duración es posible esperar el restablecimiento; después de un año no importa cuan leves sean sus síntomas, es muy dudoso el restablecimiento; después de dos años es sumamente raro el restablecimiento. La duración de la vida depende de la rapidez con que progrese la deficiencia de la función renal. Hay varios tipos clínicos: el grave o sub-agudo con hipertensión, deficiencia de la función renal y la presencia de hematuria, albuminuria y cilindruria, que producen la muerte en pocos meses; el tipo nefrótico en que el edema es la manifestación preeminente por meses y años sin hematuria, sin hipertensión y con una función renal adecuada y el tipo hipertensivo en que no hay edema o la hay muy leve y en que la orina sólo presenta alguno que otro cilindro y muy poca albúmina. El tipo nefrótico es a

veces muy difícil de distinguir de las verdaderas nefrosis y el tipo hipertensivo es a veces muy difícil de distinguir de la hipertensión esencial.

Nefroesclerosis

La nefroesclerosis que puede confundirse con la glomerulonefritis de tipo hipertensivo es en realidad y primordialmente una enfermedad de los vasos del parénquima renal por arterioesclerosis renal secundaria al síndrome conocido por hipertensión esencial. No es un proceso inflamatorio sin degenerativo. Es, anatomopatológicamente el "primary contracted kidney" que sobreviene en solamente el 10% de los casos de hipertensión esencial, sobretudo en su forma maligna. Cuando se produce suficiente esclerosis del riñón para llegar a la insuficiencia funcional de este órgano, de igual modo que en la glomerulonefritis crónica, sobreviene la uremia como fase terminal.

De modo que aunque con origen distinto y trayectoria distinta ambas, la glomerulonefritis crónica hipertensiva y la hipertensión esencial conducen a la excesiva destrucción de unidades funcionales del riñón, a la aparición del "contracted kidney" (en la una el primario en la otra el secundario) y por tanto a la uremia.

Nefrosis Necrótica Aguda

"Las nefrosis necróticas", dice Fishberg, "están caracterizadas por necrosis del epitelio renal con muy poca o ninguna injuria a los vasos renales y pueden ser causadas por varios agentes químicos, notablemente las sales metálicas del mercurio y bismuto. Entre las drogas que alguna vez producen nefrosis necrótica están el salvarsán, el veronal y el sulfonal. También el ácido clorhídrico concentrado, el sulfúrico y el oxálico." Puede ocurrir la nefrosis necrótica rara vez en la difteria, la sepsis, la fiebre tifoidea, la influenza y otras afecciones como la fiebre amarilla. De todas estas formas, la más común e importante es la nefrosis mercurial.

En este caso hay una necrosis del epitelio tubular como factor predominante, permaneciendo el glómulo intacto salvo alguna congestión e hinchazón, algunos focos de necrosis y alguna descamación del epitelio capsular. Clínicamente está caracterizada por vómitos, a veces sanguinolentos, por estomatitis, por diarrea sanguinolenta, tenesmo, albuminuria y oliguria o anuria. La gravedad específica urinaria es al principio alta, pero después cae a niveles bajos. La albuminuria no es muy marcada. Hay cilindruria y células nefróticas en la orina. En los casos fatales la muerte sobreviene por uremia. Hay durante el período de oliguria o anuria, azotemia y acidosis. Casi nunca hay edema: no siempre hay hipertensión.

Curso de la Uremia

Salvo en la nefritis aguda o en las nefrosis de los envenenamientos por bicloruro o en las obstrucciones agudas por bajo del nivel renal, la uremia es fenómeno de desarrollo lento e insidioso. Excepto en los casos producidos por obstrucción mecánica infraarenales está caracterizada por una gravedad específica urinaria baja, por altos valores azotémicos, por bajos valores de calcio sanguíneo

y por acidosis. Sus síntomas pueden clasificarse en tres categorías: cerebrales; gastrointestinales; y cutáneos.

Las manifestaciones cerebrales van apareciendo gradualmente, y son fatigabilidad, pérdida de memoria, sensación de cansancio, somnolencia —pero con insomnio—, inquietud, lenguaje confuso y pesado, desorientación y delirio terminal. Hay dolor de cabeza, sordo —no violento—, vértigo, “muscular twitchings”, alguna vez convulsiones terminales: no hay cambios en la retina, salvo por otras causas. Los síntomas gastrointestinales son: aliento amoniacal, náusea, anorexia vómitos, distensión abdominal, estomatitis, diarrea. Los síntomas cutáneos son: prurito y diversas formas de dermatosis. También hay disnea y respiración de Cheyne-Stokes. Su curso es, ya dijimos, lento, progresivo y necesariamente concluye en la muerte, apareciendo a veces a última hora una pericarditis terminal, con fiebre a veces. Hay anemia y emaciación progresiva.

Encefalopatía Hipertensiva

Hay ciertos fenómenos de carácter cerebral que han sido denominados por Oppenheimer y Fishberg “Encefalopatía Hipertensiva”, y que hasta hace poco se confundían con los fenómenos de carácter urémico por cuanto son más frecuentes que en ninguna otra condición en la glomerulonefritis aguda, pueden ocurrir también en las subagudas y en las crónicas (casi nunca en las nefrosis) y con alguna frecuencia en la hipertensión esencial, si bien rara vez en este último síndrome con la gravedad con que se presentan en los anteriores. Los fenómenos no obedecen a trastornos renales, pero coinciden con ellos muchas veces. Pueden presentarse sin embargo, con un riñón de función perfectamente normal todavía y sin alteraciones en la composición del plasma sanguíneo. Semejan un ataque eclámpico o a veces un ataque epiléptico y están caracterizados por convulsiones seguidas de coma. Se inician con prodromos tales como dolor de cabeza, vómitos y somnolencia, pérdida de apetito, debilidad física y mental e inquietud. A veces hay una gran palidez en que se pueden distinguir de ataques apopléticos.

La presión arterial está muy elevada. Puede haber alguna disminución en la excreción urinaria. Sobrevenido el ataque, hay frecuentemente pérdida de conciencia, aunque no siempre. Entre ataques, el paciente suele estar comatoso. Se distingue *prima facie* del ataque apoplético, como dijimos, en que el paciente está extremadamente pálido y en que respiración es menos estertorosa. Como la presión, según se ha dicho, está muy elevada pueden sobrevenir síntomas de insuficiencia aguda del miocardio. En tales casos la presión cae y puede sobrevenir la muerte por insuficiencia circulatoria. Puede haber disnea paroxística, pero no hay acidosis, de modo que el poder de combinar dióxido de carbono de la sangre no está reducido. Generalmente hay una presión cerebroespinal aumentada. Pueden observarse ciertos cambios retinianos, sobretudo la estrechez de las arterias de la retina, pero estos están generalmente asociados con la hipertensión. Generalmente hay papiledema. No hay azotemia, salvo que haya una deficiencia renal concomitante. Mientras en las convulsiones urémicas el calcio de la sangre está disminuido, no lo está en la encefalopatía

hipertensiva. Hay además amaurosis, delirio y afasia transitoria.

De igual modo que en un nefroesclerótico puede sobrevenir la encefalopatía hipertensiva a causa de la hiperpiesis causal, puede, aunque es menos frecuente, sobrevenir la uremia por insuficiencia renal. Igualmente en una glomerulonefritis crónica hipertensiva pueden sobrevenir los fenómenos encefalopáticos a causa de la hipertensión secundaria o sobrevenir la uremia como fase terminal.

Conviene recordar que además en ambos casos la hipertensión puede producir la insuficiencia del miocardio con insuficiencia circulatoria caracterizada por congestión pulmonar, edema pulmonar, congestión pasiva del hígado, congestión pasiva del riñón y de otros órganos y edema general agregando un elemento más de confusión en el diagnóstico.

La encefalopatía hipertensiva es un trastorno de la circulación cerebral causada por la presión sanguínea excesiva que produce, según algunos, congestión y edema cerebral, según otros, espasmos vasculares cerebrales con anemia cerebral, teoría ésta que parece más aceptable de acuerdo con los hallazgos anatomo-patológicos.

Pronóstico y Tratamiento

La uremia es generalmente un proceso lento y progresivo. Puede extenderse la vida atendiendo a mantener una circulación suficiente y una eliminación abundante. Pero el clínico se encuentra entre dos peligros:

Para aumentar la diuresis se exagera la ingestión de líquidos. Así se recarga el trabajo del corazón que por otra parte generalmente está deficiente ya y si no se aumentan suficientemente los líquidos, la poliuria no logra realizar la excreción de sólidos necesaria. El tratamiento es más que nada de régimen, reduciendo en lo posible la ingestión de proteínas, pero sin llegar a tales extremos que se agrave la desnutrición. Se debe permitir un minimum de veinte gramos de proteínas diarias, aun en los más graves, y atender los síntomas nerviosos, gástricos y cutáneos de modo sintomático. En casos de tremor muscular puede usarse el calcio. Es preciso vigilar la acidosis, pero sin caer en la alcalosis. Se debe promover la función renal hasta donde el aumento de líquidos sea permisible. También en cierto grado la excreción extrarenal. Si la anemia es profunda puede recurrirse a la transfusión.

En la encefalopatía hipertensiva los fenómenos pueden presentarse repetidas veces y merced al tratamiento de urgencia el enfermo puede salir de ellos aunque siempre amenazado de repeticiones. En los casos de nefritis aguda puede curar totalmente. El enfermo puede sucumbir ante que a fenómenos cerebrales, a la insuficiencia del miocardio o a la insuficiencia renal, pero la encefalopatía per se puede producir la muerte dentro de uno de sus ataques. El tratamiento consiste en sangrías, inyecciones intravenosas de glucosa, hipertónicas, o de sucrosa, hipertónicas (que algunos prefieren). La punción lumbar es a veces muy efectiva: otras fallas por completo. Las inyecciones intravenosas y la ingestión de sulfato de magnesio son también muy útiles. Es preciso atender a

mantener la suficiencia del miocardio y puede recurrirse a los sedantes y a los hipnóticos.

Comentarios

Quedan muchas cosas todavía por saber respecto de la hipertensión esencial con su secuela la nefroesclerosis, y también respecto de la glomerulonefritis, aguda y crónica. Así igual acerca de las nefrosis. Pero creo que se sabe bastante para establecer un esquema mental que nos permita distinguir y determinar respecto de sus relaciones con la uremia y la encefalopatía.

En primer lugar es preciso fijar claramente el concepto de nefrosis con la que se puede confundir la glomerulonefritis. La nefrosis es una degeneración renal con asiento principalmente tubular caracterizada clínicamente por albuminuria, alteración del plasma sanguíneo y edema y que no va acompañada generalmente de hipertensión, con una etiología tóxica en los casos agudos, como el de los envenenamientos por bicloruro, que puede causar uremia, o infecciosa en los casos crónicos, como en los casos de origen luético. En el otro extremo, está la nefroesclerosis que es una condición secundaria al síndrome conocido por hipertensión esencial cuya causa inmediata es la condición hipertónica de las paredes arteriolares, con hipertensión, seguida de esclerosis de los vasos renales y finalmente de fenómenos degenerativos que producen el "primary contracted kidney". Puede producir uremia y también encefalopatía hipertensiva.

En medio de ambas condiciones colocaremos la glomerulonefritis que es enfermedad primordialmente renal, inflamatoria, con destrucción de tejido renal probablemente por un fenómeno alérgico. Tiene dos etapas anatomopatológicas: la etapa del "large white kidney" caracterizada clínicamente por síntomas muy parecidos a los de la nefrosis o sea por edema y albuminuria y hematuria, y que puede estar acompañada o no de hipertensión, y con una segunda fase anatomopatológica, el "secondary contracted kidney", que se confunde con la nefroesclerosis cuando la destrucción renal ha avanzado mucho. Viene acompañada de hipertensión, bajo poder de concentración del riñón, baja gravedad específica de la orina, poliuria y finalmente uremia, o encefalopatía hipertensiva.

El hecho de que ambas condiciones presenten hipertensión, nos lleva también a tener en común los cambios retinianos hipertensivos; también a virtud de la hipertensión las repercusiones cardíacas o sea hipertrofia del miocardio, dilatación, insuficiencia, edema pulmonar y edema generalizado de origen circulatorio.

Desgraciadamente no siempre el clínico puede observar los casos desde su incipiente, ni seguir el curso y determinar la naturaleza del mismo; llegamos generalmente cuando ya los procesos han avanzado mucho. Solamente merced a una minuciosa investigación de la historia del paciente y a una observación continuada que incluya el estudio de la orina, del poder de concentración y de excreción del riñón, la lectura de la presión arterial, la observación del estado del corazón, la composición de la sangre, la condición del fondo ocular y la condición general de las arterias, puede llegarse a un diagnóstico más o menos preciso.

En todo el curso de este trabajo apenas he mencionado la arterioesclerosis. La arterioesclerosis primaria por ser fenómeno generalmente senil y que se tiende hoy a denominar mejor con el nombre de ateroesclerosis, se encuentran muchas veces en las mismas personas que pertenecen al grupo de edades en que existe una hipertensión esencial o una glomerulonefritis crónica. La glomerulonefritis sin embargo hace su aparición generalmente en personas más jóvenes. Así la nefrosis. La hipertensión esencial generalmente termina por producir una arterioesclerosis secundaria y generalizada que complica el caso.

Pudiéramos decir que la nefrosis y la glomerulonefritis aguda son más generalmente enfermedades de la niñez y de la juventud; que la glomerulonefritis crónica se encuentra también en esas edades y se encuentra con más frecuencia en edades superiores; que la hipertensión esencial y arterioesclerosis y nefroesclerosis son generalmente enfermedades de la edad madura y que la ateroesclerosis es enfermedad de la vejez; pero una persona madura, por ejemplo, bien puede presentar el cuadro de una glomerulonefritis crónica, de una hipertensión seguida de arterioesclerosis y de una ateroesclerosis concomitante. Hay mucho que investigar todavía en todas estas condiciones.

COMENTARIO

Manuel Martínez Maldonado, MD, FACP*

Este artículo escrito en 1939 (¡hace 50 años!) revela una serie de datos históricamente interesantes a la vez que, desde el punto de vista médico, curiosos. El Dr. Fernós Isern no suple una bibliografía, de modo que se dificulta discernir el origen de las aseveraciones en el escrito. Es evidente, sin embargo, que Fernós conocía los escritos de A.M. Fishberg probablemente su libro *Hypertension and Nephritis*, publicado por Lea and Febiger, en el año 1939. Además, hace referencia al clásico por Oppenheimer y Fishberg en *Archives of Internal Medicine* (41:264, 1928), en el que se acuñó el término encefalopatía hipertensa.

En los años 30 no se llevaban a cabo biopsias renales percutáneas, de modo que las causas de uremia indicadas por Fernós se reducen a las que se veían frecuentemente en autopsia. Por lo tanto las agrupa como Nefritis Aguda y Crónica, Nefroesclerosis (hipertensión) y Nefrosis necrótica (lo que conocemos hoy como necrosis tubular aguda). Por supuesto que esto ha cambiando según la nefrología (palabra de origen tan reciente como 1968) ha evolucionado en una nueva disciplina de la medicina interna, y los diagnósticos, en su mayoría, se establecen *ante-mortem*.

Al momento de la publicación, Fernós no tenía la ventaja de conocer los estudios seminales de fisiología renal que condujo Homer Smith, ni los conceptos anatómico-patológicos estructurados por Jean Oliver. Sin embargo, en el contexto inevitablemente empírico que infectaba la medicina antes de la Segunda Guerra Mundial, algunas de sus sentencias son de actualidad.

Aparte de su descripción textual de la uremia y sus causas, Fernós advierte sobre el peligro de intentar la inducción de una diuresis exagerando la ingestión de líquidos. Este llamado al juicio racional en el manejo del paciente es necesario aún hoy día en situaciones en que se desconoce la patofisiología del síndrome de insuficiencia renal crónica.

Es de interés también el llamado de Fernós a que se limite la ingestión de proteínas, acción terapéutica que se ha puesto de moda en los últimos años y que es motivo de intensa investigación por parte de muchos investigadores (incluyendo éste que escribe).

Por otro lado, las recomendaciones de punción lumbar, la ingestión de sulfato de magnesio para encefalopatías hipertensas/urémicas, son peligrosas, y están absolutamente contraindicadas.

En general, el contenido del discurso del Dr. Fernós Isern, era lo aceptable para su época, y sus errores consecuencias del empiricismo que aún aquejaba la medicina de la ante guerra en los años 30.

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MEDICAL ASPECTS OF NUTRITION

Recent Advances in the Management of Lactose Intolerance*

Dennis A. Savaiano, PhD**
Catherine Kotz, BS*

Dairy foods are an important source of high-quality protein, riboflavin and calcium in the diets of children and adults in the United States, Canada, Europe and other countries with a dairy industry. However, up to 70% of the world's population may develop gastrointestinal symptoms, including excessive gas production, pain and diarrhea following consumption of lactose-containing dairy foods. Young mammals, including humans, have a high level of lactase activity in the lining of their upper intestine, since they depend on lactose as the primary carbohydrate in their diet. As mammals mature and are weaned, lactase activity in the intestine is greatly reduced. Like other mammals, most humans (approximately 70%) lose the majority of their intestinal lactase activity after weaning. Individuals who lose their intestinal lactase have been described as lactase-deficient, lactase non-persistent or lactose malabsorbers.

What is unique is that a small portion of the world's population (approximately 30%, including descendants of some African and Middle Eastern tribes and most Northern Europeans) have apparently adapted to maintain the lactase enzyme. Research strongly suggests that this adaptation is genetically controlled, permanent and is related to the development of dairying in these regions of the world several thousand years ago.¹

For those individuals who maintain the lactase enzyme, eating dairy foods will not cause lactose intolerance problems. But individuals who are lactase nonpersistent will malabsorb a significant portion of a dietary load in the small intestine. Lactose which is not digested in the small intestine reaches the large intestine where it is digested by the microflora, forming lactic acid, shortchain fatty acids (SCFA) and hydrogen gas. The

SCFAs are rapidly absorbed by the intestine and are a source of energy. Presumably, when the lactose concentration of the large intestine exceeds the ability of the bacteria to digest it, osmotic pressure results in increased motility, pain, loose stool and diarrhea. The purpose of this article is to provide an overview of the recent research findings relating to the dietary management of lactose intolerance.

Lactose Intolerance Symptoms Are Related to the Amount of Lactose Consumed

Scientists and clinicians have recognized for some time that the majority of lactose malabsorbers will not develop symptoms of intolerance following the consumption of a single 8-ounce serving of milk containing approximately 12g of lactose. Newcomer and McGill,¹² Savaiano and Levitt³ and recently Scrimshaw and Murray⁴ have reviewed the research findings relating dose of lactose to the development of symptoms with the uniform conclusion that, at most, only one-fifth to one-third of malabsorbers will develop symptoms following this physiological dose of lactose.

Further, the level of symptoms response to one glass of milk is not very different from that observed with lactose-free, flavored placebo beverages,⁵ although such controls may be criticized for their high osmotic loads. Increasing the dose of lactose to 24g (found in two glasses of milk) increases the incidence of symptoms to a range close to 50%. Increasing the dose further, toward 50g of lactose (approximately one liter of milk) increases the incidence and severity of symptoms. A 50g lactose load has been used historically to test for the presence of lactose malabsorption. Unfortunately, the extensive and relatively severe symptoms resulting from this unphysiologic lactose load have tended to develop and reinforce the misconception that any lactose load will cause symptoms in lactose malabsorbers.

A corollary to this misconception is the unfounded belief that all dairy foods will cause lactose-intolerance symptoms. Lactose is a water-soluble disaccharide which

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remains primarily with the whey portion of dairy foods. As such, hard cheeses (with the whey removed from the curds) contain very little lactose (Table 1).³ Cottage cheese, ice creams and yogurts contain reduced amounts of lactose relative to milk and therefore cause fewer symptoms. A special attribute of yogurt, its microbial beta-galactosidase, which assists the digestion of lactose *in vivo*, will be discussed later in this review.

Table 1

Lactose in Common Dairy Foods

Food	Lactose (percent)
Cow's milk	
Whole	4.7
Skim	5.0
Yogurt (lowfat)	4.0-4.6
Cream	3.0
Cottage cheese	1.4
Hard cheeses	trace
Ice cream (14% fat)	3.6
Milk chocolate	8.1

(Savaiano and Levitt, 1987)

Ingestion of Lactose with Other Nutrients Reduces Intolerance

The quality and type of foods consumed along with lactose appear to be a second important factor in determining the incidence of symptoms. In controlled experiments evaluating lactose intolerance, researchers have typically fed lactose in water or milk. Such experimental designs probably result in a higher incidence of symptoms than the typical consumer might experience, since consumers often drink milk with other foods.

In 1973, Leichter convincingly demonstrated reduced malabsorption and improved tolerance to lactose consumed in whole milk as compared to skim milk or water.⁶ Pirk and Scala⁷ reported that in malabsorbers, stomach emptying is delayed with lactose (versus sucrose) feeding, whereas small intestinal transit is more rapid. Chocolate milk also appears to delay stomach emptying, presumably due to the greater osmotic load.⁸ The delay in gastrointestinal transit of lactose by other nutrients appears to be significant in slowing malabsorption and reducing the development of intolerance symptoms. Both Solomons, et al.⁹ and Martini and Savaiano¹⁰ have recently published experiments showing delayed transit of lactose to the colon (as measured by breath hydrogen) when lactose is consumed with a meal. In Martini and Savaiano's study, both the severity and incidence of symptoms were reduced three-fold so that only 25% of the subjects experienced symptoms of any kind following a 20g lactose load consumed with a breakfast meal (Table 2).¹⁰

Table 2
Ranking of Severity and Number of Subjects with Intolerance Symptoms*

	Meal				
	Acqueous Lactose	Skim Milk	Food Supplement	Breakfast Meal	Breakfast + Supplement
Lactose	19g	12g	19g	0g	19g
Mean	3.17	2.00	2.17	0.8	0.83
+/- sem	+/- 0.42	+/- 0.49	+/- 0.52	+/- 0.08	+/- 0.47
Number subjects with symptoms	12/12	8/12	9/12	1/12	3/12

*Ranking of severity of symptoms:

0. No symptoms
1. Mild gas and/or borborygmi
2. Excessive gas
3. Severe gas and/or cramps
4. Loose stools
5. Severe diarrhea

(Adapted from Martini and Savaiano, 1988)

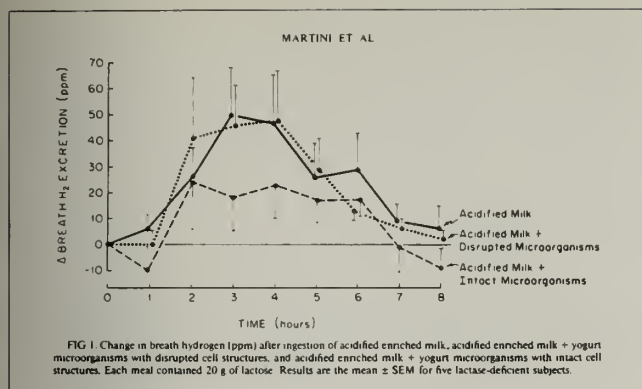
Lactose Digestion from Yogurts and Other Fermented Dairy Foods

Since the work of Gallagher, et al.¹¹ and Alm¹² in the 1970s, it has been suggested that fermented dairy foods may be tolerated better than similar unfermented products. Several reasons were typically invoked to explain the phenomenon including the lower lactose levels found in these foods¹² and the contribution to digestion that lactic acid bacteria might make.¹³ Work by Kilara and Shahani¹⁴ and Goodenough and Kleyn¹⁵ indicated that the bacteria used in yogurt cultures (*Streptococcus thermophilus* and *Lactobacillus bulgaricus*) contain a betagalactosidase activity and that this activity could possibly enhance lactose digestion *in vivo* in the rodent gastrointestinal tract. Such findings led Kolars, et al.¹⁶ and Gilliland and Kim¹⁷ to evaluate lactose digestion from yogurt containing controlled amounts of lactose.

In January of 1984, both groups reported a significant reduction in malabsorption as measured by breath hydrogen production. In addition, Kolars, et al. were able to demonstrate a significant reduction in intolerance symptoms with yogurt feeding and the presence of yogurt beta-galactosidase activity in the duodenum of yogurt-fed subjects.¹⁶ The enhanced digestion of and tolerance to lactose from yogurt has been replicated by several investigators.¹⁸⁻²⁴ In contrast, a recent study failed to show a significant reduction in symptoms following yogurt feeding, apparently due to a low level of symptoms resulting from the control lactose load.²⁵

The mechanism by which the yogurt-borne microbial beta-galactosidase can facilitate lactose digestion *in vivo* in the gastrointestinal tract is not completely understood. It appears that an intact microbial cell structure is critical for the survival of the enzyme during gastric digestion.¹⁹ Sonication or heating to disrupt the cell structure significantly elevates malabsorption while reducing the survival of the enzyme *in vitro* (Figure 1)^{17, 19} The pH of the stomach may be a second critical factor since the yogurt culture beta-galactosidase is rapidly destroyed *in vitro* at pHs ≤ 3.0 .¹⁹

It should be further noted that yogurt is an excellent buffer of acid, due to its casein, lactase and calcium phosphate content. This buffering capacity may keep portions of the stomach above pH 3.0 following ingestion



of a yogurt meal.¹⁹ Once the intact yogurt bacteria enter the small intestine, bile acids are hypothetically able to disrupt the cell structure, releasing enzyme into the luminal contents. *In vitro*, bile will disrupt yogurt bacteria, releasing beta-galactosidase activity.¹⁷ However, the *in vivo* action of physiological concentrations of bile acids on yogurt bacteria has not been demonstrated.

The beta-galactosidase from yogurt culture is sensitive to freezing. After one week, beta-galactosidase activity fell to 34% of the original activity when yogurt was frozen at -14 C and to 73% of the original activity when frozen at -70C.²⁰ Commercially manufactured frozen yogurts apparently vary from no betagalactosidase activity²⁰ to activities observed with the freezing of fresh yogurt.²⁶

Results from Savaiano, et al. indicate that cultured milks ("buttermilks") do not improve lactose digestion or reduce intolerance symptoms among lactose malabsorbers, probably because of the different lactose metabolizing pathway found in the lactic acid bacteria used to formulate these products.¹⁸

Cultured milks are typically fermented with *Streptococcus lactis* or *Streptococcus cremoris* and *S. lactis* subspecies *diacetylactis*. These microbes have a phospho-beta-galactosidase which utilizes phosphorylated lactose as a substrate.²⁷ The phosphorylation requires a functional permeability system (intact cell membrane).²⁷ Apparently, there is either insufficient phospho-beta-galactosidase in cultured milk or more likely, the cell membrane phosphorylation system is disrupted during digestion, thus preventing significant digestion of lactose *in vitro*. Disruption of the cell structure *in vitro* by sonication results in only trace "lactase" activity in cultured milks.¹⁸

Lactose Digestion from Unfermented Acidophilus Milk

Several research groups have evaluated the ability of unfermented milk containing *Lactobacillus acidophilus* to modify lactose digestion and the development of intolerance symptoms.^{18, 28, 29, 30} *L. acidophilus* strain NCFM has been most extensively studied. This strain is derived from human fecal samples, has been available commercially for several years and synthesizes a beta-galactosidase.^{31, 32}

In 1981, Payne, et al.²⁸ reported no improvement in lactose malabsorption after feeding commercially available acidophilus milk for one or eight days. Unfortunately, the number of viable lactobacilli and the beta-galactosidase activity of the product were not evaluated. Utilizing defined acidophilus products with 10⁶, 10⁷ or 10⁸ viable NCFM strain lactobacilli per ml, Kim and Gilliland in 1983 showed a moderate but significant reduction in initial breath hydrogen production (approximately 15-20ppm) with the 10⁶ (two experiments) and 10⁸ doses but no improvement with the 10⁷ dose.²⁹ Breath hydrogen production was measured for only 3-4 hours after the test meal. Feeding acidophilus milk for eight consecutive days did not improve the absorption beyond that observed with a single meal. Unfortunately, Kim and Gilliland did not report intolerance symptoms nor did they measure the beta-galactosidase activity of the products. Newcomer, et al., also in 1983, reported no improvement in intolerance symptoms with the substitution of acidophilus milk (10⁶ cells/ml of the NCFM strain) for milk in mixed diets of lactose malabsorbers.³⁰ Milk (or acidophilus milk) intakes varied from 0.25 to 4.5 glasses per day in a randomized, double-blind, cross-over design. Each treatment lasted one week. Symptoms were identical for the acidophilus milk and control milk periods. No estimate of lactose malabsorption was made in this study.

In 1984, Savaiano, et al. reevaluated the possible improvement of lactose digestion from acidophilus milk manufactured using frozen concentrates of the NCFM strain (standard manufacturing procedure).¹⁸ The product contained 10⁷ cells/ml. No improvement in lactose digestion (as measured by breath hydrogen) of relief from intolerance symptoms were observed. Interestingly, the acidophilus milk contained no detectable beta-galactosidase activity. Recent knowledge regarding the activity of beta-galactosidase from yogurt cultures indicates that active cultures in long or stationary phase of growth (as in yogurt) contain substantially elevated beta-galactosidase activity.^{20, 33, 34} Activity is rapidly lost with freezing, although cell counts remain fairly constant. Cell wall and membrane damage of *L. acidophilus* during freeze drying and vacuum drying has been documented.³⁵

It is likely that the lack of success in formulating effective acidophilus milks may be, at least in part, due to the use of frozen concentrate starter cultures. Another potential variable which could alter the activity of beta-galactosidase in the intestinal tract is the bile sensitivity of the strain. Gilliland, et al.³⁷ have shown that growth rates of *L. acidophilus* strains vary considerably in bile-containing media. Theoretically, a bile-sensitive strain would be more likely to release its beta-galactosidase *in vivo*, thereby aiding lactose digestion. In accord with this hypothesis, McDonough, et al. recently reported the improved digestion of lactose from sonicated acidophilus milk.²¹ The product was formulated from frozen concentrates (NCFM strain, 10⁸ cells/ml) and sonicated to disrupt the cell structure just prior to consumption. The release of beta-galactosidase reduced breath hydrogen production from 28ppm to 12ppm, suggesting that bile-sensitive strains, where beta-galactosidase is released *in vivo*, could be effective in improving lactose digestion.

Enzyme Tablets

An additional approach to prevent intolerance symptoms is the use of commercially available lactose-digesting enzyme tablets. Several brands are commonly available. If instructions are followed, these products appear to be effective in reducing and/or eliminating symptoms. The tablets are either added to milk the night before drinking to predigest most of the lactose or they are taken with the dairy food (sprinkled over ice cream for example) and work in the stomach or intestine to supplement the body's lactase just like yogurt. Experiments confirm the effectiveness of these enzyme preparations either as a means of producing low-lactose milk^{28, 38, 39, 40, 41} or as a dietary adjunct.⁴²⁻⁴⁵

Colonic Adaptation to Lactose

As described by Scrimshaw and Murray,⁴ lactase-deficient persons who routinely eat lactose-containing foods adapt to exhibit fewer symptoms.⁴⁶⁻⁵⁰ Such observations result, in part, from research aimed at determining if the mammalian small intestinal lactase can adapt to the long-term ingestion of lactose. It appears that the mammalian lactase is a nonadaptable enzyme.^{46, 51} However, incidental to these findings, researchers noted that both rodents and humans exhibit fewer symptoms of intolerance after "adapting" to a lactose-containing diet. Studies in rodents,⁵² chickens⁵³ and pigs^{54, 55} also show that the large intestine bacteria adapt to ongoing lactose-containing diets. Fecal microbial beta-galactosidase increases three- to six-fold in such experiments. Concurrent with this increase in lactose-digesting capacity is a reduction in malabsorption symptoms. Whether this increased enzyme activity is due to induction in existing microbes or an alteration in the microbial population is not known.

In humans, Florent, et al.⁵⁶ have completed elegant work showing similar adaptation to lactulose. Lactulose is a nondigestible disaccharide of fructose and galactose. Administration of 20g of lactulose twice per day for eight days resulted in a six-fold increase in fecal beta-galactosidase activity, increased cecal ¹⁴C-lactulose oxidation, lactic acid and SCFA production and a reduction in breath hydrogen production. In a followup study,⁵⁷ adaptation to lactulose resulted in slower transit times and reduced incidence of diarrhea from a single lactulose load. Similar controlled experiments with lactose feeding are not available, but recent studies suggest that lactose digestion may improve during pregnancy⁵⁸ (when milk consumption might be increased) and worsen with aging⁵⁹ (when milk consumption might decline). The role of the large intestine bacteria in these reported adaptations is unknown. Additional research is needed in order to determine if the intestinal bacteria hold the key to preventing the gastrointestinal intolerance symptoms that can occur in lactase-deficient persons.

Lactase Nonpersistence, Lactose Consumption and Calcium Absorption

Interest in the effect of lactose on calcium absorption among lactose malabsorbers has grown with the recognition that a significant portion of patients with

osteoporosis also exhibit signs of lactose malabsorption.⁶⁰⁻⁶⁴ Early research on the influence of lactose on calcium absorption among lactose malabsorbers is inconsistent, showing both improvement⁶⁵ and reduction in calcium availability.^{66, 67} In 1973, Kocian, et al.⁶⁸ reported that the consumption of 39g of lactose (as compared to 39g of glucose) resulted in a delayed⁴⁷ calcium absorption among young adult lactose malabsorbers. In contrast, calcium absorption was more rapid with lactose consumption among lactase-persistent subjects. However, the overall retention of labeled calcium (measured after 7 days) was not different between absorbers and malabsorbers, suggesting only a slowed rate but not a reduction in the absolute amount of calcium absorbed.

In 1983, Cochet, et al.⁶⁹ using duallable methods, found a reduction in total fractional calcium absorption from 0.255 to 0.209 ($p < 0.005$) when the calcium was fed with 50g of lactose to young adult malabsorbers. In lactase-persistent adults, 50g of lactose increased total fractional calcium absorption from 0.224 to 0.356 ($p < 0.001$). Using physiological doses of lactose (7.5g to 10.3g) in milk, Smith, et al.⁷⁰ reported no difference in ⁴⁵calcium absorption between lactose malabsorbers and lactase-persistent adults. Further, malabsorbers absorbed slightly more calcium from yogurt than did lactase-persistent adults ($p < 0.05$). Although the number of subjects studied was small ($n=7$ malabsorbers, $n=5$ controls), these results suggest that malabsorbers do not absorb less calcium from typical servings of dairy foods. Using double-label techniques, Tremaine, et al.⁷¹ found similar results when either 240ml of milk (containing a approximately 10-12g of lactose) or lactose-hydrolyzed milk was fed to 10 lactase-persistent and 10 lactase-nonpersistent adults. No differences in calcium absorption were observed between milks, whereas lactose malabsorbers absorbed significantly more calcium from both milks ($p < 0.01$), possibly reflecting lower dietary calcium intakes. In summary, these studies suggest that physiological doses of lactose do not inhibit calcium absorption among lactose malabsorbers. However, large unphysiological doses of lactose, possibly due to intestinal secretions and/or shortened transit times, may reduce calcium uptake.

Summary

Lactose intolerance is a concern for the majority of the world's population. Persons who experience symptoms following the consumption of milk should consult with their physician. Symptoms may be eliminated or reduced with good dietary management that includes:

1. limiting milk consumption to one glass at a time
2. drinking milk with other foods rather than alone
3. eating yogurts instead of fluid milk
4. using enzyme tablets to predigest the lactose in milk or to supplement the body's own lactase
5. possibly eating small amounts of dairy foods each day to adapt the colonic bacteria

For an additional review of the research findings on lactose intolerance and milk drinking, the reader is

directed to reference 4, a very recent and complete review by Scrimshaw and Murray. For information on dietary management of lactose intolerance suitable for the consumer, contact your local affiliate of the National Dairy Council.

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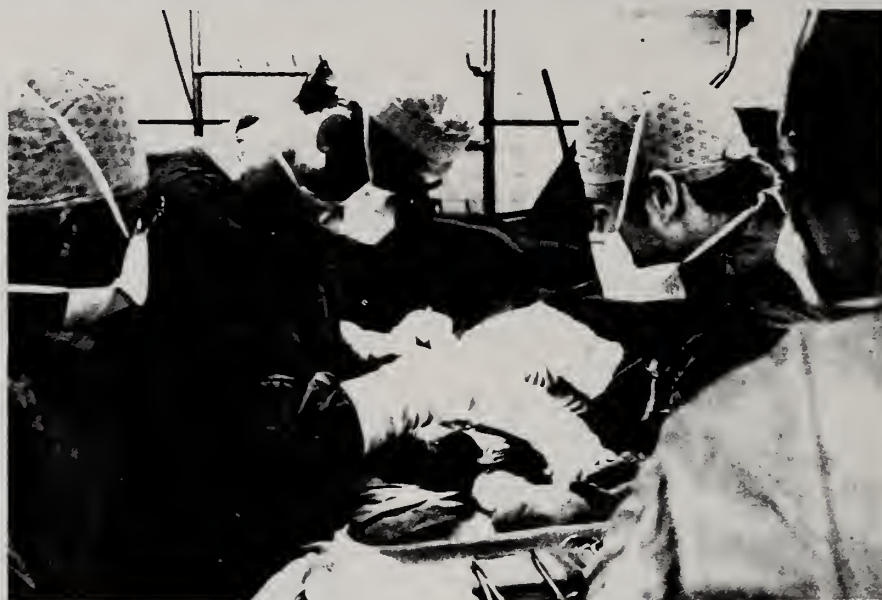
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ACTIVOS

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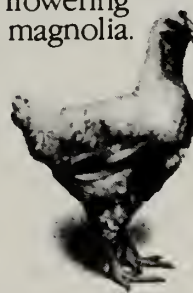
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1. I think I have lumbago.
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3. I'm on the grapefruit diet.
4. I gave six months ago.
5. I just got back from Monaco.
6. The lines are thirteen blocks long.
7. My mother won't let me.
8. I didn't sign up.
9. I'm going out of town.
10. Asthma runs in my family.
11. I forgot to eat this morning.
12. I'm allergic to flowering magnolia.



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USE OF LASERS IN HUMAN CORONARY ARTERIES EXAMINED

Laser balloon angioplasty is now a clinical reality, reported reality, reported J. Richard Spears, M.D., and colleagues at Harper Hospital and Wayne State University in Detroit. They described their experience with this technique in seven patients who first underwent conventional elective PTCA using a 3.0 mm balloon. Laser angioplasty was then performed using a 3.0 balloon catheter and a Nd:YAG 1.06 micron cw laser delivery system on the same coronary segment. A 20 second laser dose was applied in a cylindrical pattern over the 1.5 cm midportion of the balloon. This was calculated to provide a temperature of approximately 100 degrees C, 1 mm from the balloon surface. Mean stenosis diameter, as calculated by computer assessment of digitized cine frames, increased from 2.17 ± 0.72 to 2.61 ± 0.26 mm. There were no complications and no change in stenosis diameter was noted in repeat studies at 24 hours or, in three patients, at one month.

Thomas J. Linnemeier, M.D., and colleagues at St. Vincent's Hospital, Indianapolis, Ind., reported on a multicenter experience with laser-assisted angioplasty of mid-body saphenous vein graft lesions. Sixteen grafts ranging in age from 1 to 11 years were dilated: 1 LAD, 8 LCx and 7 RCA. A Trimedyn® argon laser delivered 8 to 12 watts of energy; conventional PTCA followed. Adequate patency was achieved in 14 of 15 vessels; one patient developed tamponade, required early emergency CABG and subsequently died. The patient with the failed PTCA also died later and there was one distal embolization. At followup several months later, there were two restenoses and the remaining patients were asymptomatic.

The same investigators, led by Timothy A. Sanborn, M.D., of Mt. Sinai Hospital, N.Y.C., reported results on 19 patients with coronary lesions (11 LAD, 4 LCx, 4 RCA) who underwent laser-assisted angioplasty followed by conventional PTCA. There were no perforations or

embolization, and laser recanalization was possible in 17 of 19, all of whom had successful conventional PTCA immediately thereafter. There was one abrupt closure, two early (2-5 days) closures, and three restenoses.

BETA BLOCKADE AND MITRAL VALVE DISEASE

Is beta-blockade efficacious for reducing symptoms in patients with compensated mitral stenosis (MS)? No, say Thomas L. Ashcom, M.D., and associates at Brooke Army Medical Center, Houston, Tex. They studied eight patients with MS treated with beta-blockers and six controls with MS not on beta-blockers. Simultaneous right and left heart pressures (recorded with micromanometer catheters), pulmonary capillary wedge pressure (WP) and cardiac output (CO) were recorded at rest and during supine bicycle exercise. In controls, the resting and exercise heart rates averaged 79 and 112, respectively. In patients on beta-blockers, the corresponding values were 70 and 88. Beta-blockade reduced both resting CO (4.0 vs. 5.0 L/min) and exercise CO (4.7 vs. 6.9 L/min). Though resting WP was similar (averaging 19 mm Hg), beta-blockers reduced exercise WP (27 vs 35). Mitral valve gradients were comparable at rest (11 vs. 14) but reduced by beta-blockers at exercise (19 vs. 24).

The authors concluded that betablockade fails to prevent most of the exercise-induced elevation in WP and significantly limits exercise cardiac output and they advised caution in its use in these patients.

Mitral Valve Prolapse

Mitral valve prolapse (MVP), always a vexing entity, is common in connective tissue diseases. Steven L. Comens, M.D., and associates at the University of Missouri Health Sciences Center at Columbia, studied 24 patients with SLE, 28 with scleroderma, 36 with mixed connective tissue disease, (MCTD) and 110 normal age and sex-matched controls. MVP was diagnosed if late systolic hammocking of one or both mitral leaflets were seen on M-mode echocardiogram, and/or posterior systolic arching of one or both mitral leaflets in the parasternal long axis or 4-chamber 2-D echocardiogram. The frequency of MVP by disease was: SLE, 38%; scleroderma 36% (similar for CREST and non-CREST variants); and mixed connective tissue disease, 30%. Only 10% of controls had echocardiographic evidence of MVP.

The authors concluded that MVP occurs with disproportionately high frequency in SLE, scleroderma (CREST and non-CREST variants) and MCTD.

Endocarditis

In a case-control study of 48 patients with native mitral valve endocarditis seen at the CHU Nancy-Brabois, France, Nicholas Danchin, M.D., et al found an 18%

incidence of pre-existing MVP (vs. 6% in a healthy age and sexmatched control population). The relative risk of endocarditis was 3.3 for all patients and 16.2 in those with a systolic murmur—confirming the clinical examination as a reliable marker of those who need antibiotic prophylaxis for procedures likely to cause bacteremia. In those without a murmur, it remains speculative as to the necessity and risk/benefit ratio of antibiotics.

Louis A. Cannon, M.D., and colleagues at Akron General Medical Center, Akron, Ohio, studied 21 patients (all comers—not those with MVP) intubated emergently in the emergency room setting. Several post-intubation blood cultures obtained within 30 minutes were positive: 29% in the 14 patients who were nasotracheally intubated—all with nasopharyngeal flora—and none of seven who were orotracheally intubated.

The researchers summarized that there is significant risk of bacteremia associated with emergency NT intubation which may be accompanied by organisms producing serious morbidity. They suggest prophylaxis for patients at risk for infectious endocarditis.

DILTIAZEM FOUND USEFUL LONG TERM AFTER NON-Q-WAVE MI

Data presented at the American Heart Association meeting supported the long-term use of diltiazem prophylactically after non-Q-MI. William E. Boden, M.D., and associates, reporting for the Multicenter Diltiazem Post-Infarction Trial Study Group, analyzed recurrent cardiac events in a group of 634 such patients who were randomized to diltiazem, 60 mg. four times daily, or placebo. The mean follow-up was 25 months (range, 12-52). The mean patient age was 59 years; 76% were male, 81% had an LVEF 40%, and 17% had pulmonary congestion on chest x-ray. During the follow-up, the cumulative 1-year cardiac event rate was 15% in the placebo group and 9% in the diltiazem group ($p < 0.03$). This extends the previously recognized benefit of diltiazem in the in-hospital period to the 1-year mark.

From the same study, J. Thomas Bigger, Jr., M.D., of Columbia University evaluated the effect of diltiazem on ventricular ectopy. Holter monitor recordings were obtained in 1603 post-MI patients (Q-wave and non-Q-wave) three months after the index event. Though there was mild heart rate slowing, no differences were detected in any VPD frequency or characteristics. The authors concluded that diltiazem had no significant effect on ventricular arrhythmias after MI, perhaps explaining its failure to influence overall mortality in unselected patients.

Is there a role for beta-blockers in non-Q MI? Mihai Gheorghiadu, M.D., et al analyzed data from the Beta Blocker Heart Attack Trial (BHAT). Half of the 601 patients without Q waves received propranolol 180-240 mg/day and half, placebo during their initial hospitalization. At a median follow-up of over two years, there were no significant benefits seen with respect to

death, rate of reinfarction, angina, or CABG. The incidence of heart failure was greater for patients on propranolol than placebo (12.6% vs. 7.6%, $p < 0.04$). Thus, retrospective analysis of the BHAT data failed to indicate that propranolol is of prophylactic benefit in non-Q-MI.

THE LATEST ON AIDS AND HEART DISEASE

As the number of cases of AIDS and AIDS-related illnesses continues to increase, more and more patients are experiencing cardiac manifestations of their disease. Five reports from the recent American Heart Association meeting in Washington, D.C., high-light these findings.

R. Lee, Vogel, M.D., and colleagues at Children's Hospital, Newark, N.J., reviewed the cardiac status of 1975 children with perinatally-acquired HIV antibody and found five cases of congenital heart disease. Findings were clinically evident in four and uncovered echocardiographically in the fifth. The defects uncovered included one case each of ASD, tetralogy of Fallot, ventricular septal defect (VSD, VSD with pulmonic stenosis and tricuspid atresia. Three children required surgical correction of the lesion. Only two of the five had clinically evident AIDS. In comparison to the general population, in which there is a 0.4% incidence of congenital heart disease, there was a 2.8% incidence in this population, leading the authors to conclude that 2-D echocardiography should be performed on all such children.

Echocardiographic Findings

Expanding upon the echocardiographic findings in AIDS patients was W.S. Chung and associates at the University of California, San Francisco. They examined 64 patients with HIV (70% of whom had full clinical AIDS and 94% of whom were homosexual) and 20 controls with leukemia. Dilated cardiomyopathy (DCM) was present in seven and was clinically occult in three; pericardial effusion was noted in six, one of whom had early tamponade. Most abnormalities occurred in hospitalized patients; DCM was more common in AIDS patients than in controls and patients responded to digoxin and diuretics.

Selenium Deficiency

At the Claude Bernard Hospital in Paris, Antoine Lafont, M.D., et al found a selenium deficiency, presumably due to malnutrition, in seven of nine consecutive patients with AIDS and DCM. Treatment with sodium selenite (800mcg/dx15d, then 400 mcg/d) reversed LV dysfunction in six of seven patients within two weeks.

The overall prevalence of cardiac findings was examined by Warren S. Levy, M.D., and co-workers at George Washington University (Washington, D.C.). Sixty consecutive patients were studied: 25 seropositive for HIV without AIDS, 24 with AIDS and opportunistic infections and 11 with AIDS without such infections. Echocardiography, Holter monitoring and ECG were performed on most patients. LV dilatation, LV hypoki-

nesis and pericardial effusion were found in nine patients. Repolarization abnormalities were found in 26% of subjects but Holter abnormalities were present only in three patients, all of whom had abnormal echocardiograms. The incidence of abnormalities was present in 12 of 22 patients with low T4 lymphocyte counts vs. one of 14 patients with higher T4 counts ($p < 0.01$), but did not differ by clinical status. These data suggested a role for HIV as a direct cardiac pathogen. In a study of 115 consecutive patients at the Claude Bernard Hospital, Dr. Lafont et al found echocardiographic abnormalities in 72% of AIDS patients but $< 30\%$ of those with AIDS-related complex or without symptoms. Performing echocardiography at the AIDS stage of the illness will result in a higher yield than when done in the ARC stage.

ANTI-ARRHYTHMIC DRUG UPDATE

Quinidine-Encainide Interaction

Workers at Vanderbilt University assessed pharmacokinetics of encainide and quinidine in eight subjects. Even at low doses, quinidine inhibited encainide metabolism and reversed its ECG effects in those with the extensive metabolizer phenotype. This suggests that caution be used when a patient is started on quinidine while already taking encainide.

Amiodarone

At McMaster University, Canada, John A. Cairns, M.D., and associates randomized 54 post-MI patients with frequent ventricular ectopy (> 240 VPD/day on Holter monitoring done 5-30 days after the infarct) to receive either placebo ($n=18$) or amiodarone ($n=36$). The latter was given at a dose of 10 mg/kg/day for three weeks, followed by 300-400 mg/day; it was further reduced at four month intervals if VPD's were suppressed. Effective VPD suppression (90% reduction if > 720 VPD/day; 80% if < 720 /day) was seen in 82-88% of patients taking amiodarone at two weeks to eight months after the MI and in 77% of the patients evaluated at 12 months. Placebo-treated patients met the efficacy criteria 8% of the time at two weeks, 50% at two months, and from 14-33% of cases at 4-12 months. By eight months, the mean effective amiodarone dose was 200mg/day and VPD's were markedly reduced compared to baseline. This suggests that amiodarone should be studied further at a safe, effective dose for high-grade post-MI arrhythmias.

Beta-Blocking Effects of Drugs

Data was presented to demonstrate that both amiodarone and propafenone have significant and clinically relevant beta-adrenergic blocking activity.

Sotalol

D-sotalol, an isomer of dl-sotalol, was shown to be devoid of beta-blocking activity both in vivo and in vitro; it has 450-fold less affinity for lymphocyte beta-2 recep-

tors than does propranolol. At Sequoia Hospital, Redwood City, CA, investigators Michael A. Ruder, M.D., et al treated 65 patients with sustained, drug refractory VT or VF with oral sotalol. The drug was ineffective in 11 patients, as manifest by continued inducibility at EPS. In the remaining 54, followed for nearly one year, 24 had concurrent placement of an AICD. The actuarial incidence of success with sotalol was 47% at one year. At follow-up EPS, VT/VF induction was prevented in only 20%; clinical recurrences occurred in 17% of those who were non-inducible and 44% of those who were inducible. Side effects necessitating withdrawal of drug occurred in 22% dose reduction after discharge was required in another 15%. Arrhythmia exacerbation occurred in 6/54 patients (11%) and CHF worsened in nine (17%). Only one patient died suddenly while on sotalol. The authors concluded that though sotalol was effective in a large proportion of patients, "there is a high rate of limiting side effects and a substantial risk of arrhythmia exacerbation".

AMERICAN COLLEGE OF PHYSICIANS



ACP RECOMMENDS CONSERVATIVE APPROACH TO TESTING FOR ALLERGIES

Allergy testing should be used to verify diagnoses based mainly on a patient's symptoms and medical history, according to the American College of Physicians (ACP).

"Allergy Testing," a position paper published Feb. 15 in *Annals of Internal Medicine*, recommends when to use various kinds of allergy tests. All tests should be interpreted only in light of the patient's history and symptoms, the paper states.

The impetus for the statement, in part, is the large number of allergens available for testing. Some physicians have made as many as 300 pricks in the skin of a single patient, using one allergen at a time to single out the source of an allergic reaction, the authors wrote.

The paper, developed by ACP's Clinical Efficacy Assessment Project (CEAP), evaluates three categories of tests: skin, provocation and in-vitro.

The skin-prick test is generally the best for clinical use of all methods currently employed, according to the paper. The widely used test, administered by a small needle that is passed through a drop of the test allergen, is specific, sensitive, safe, convenient and economical, ACP stated.

A second skin test, the intradermal test, is less accurate and slightly less safe than the skin-prick method, according to the paper. A third skin test, the titration test, should be used only to determine a safe starting dose of anti-allergy medication, the paper states. The patch test, a fourth skin test, is safe and reliable if properly done by

experts for allergies to cosmetics, costume jewelry, dyes and salves.

Two provocation tests evaluated, bronchial and oral, are used to provoke signs and symptoms of allergic reactions to certain substances. ACP stated that the bronchial provocation test should be used only for research because it is expensive, time-consuming, uncomfortable and carries a risk of severe asthmatic reaction. The oral provocation test has broader uses than the bronchial test, according to the paper. It detects both true allergy and intolerance, but must be carefully administered and analyzed to avoid misinterpretation, the paper states.

An in-vitro test, the specific IgE test, is valuable for research, ACP stated, but less sensitive, more expensive and more time-consuming than the skin-prick test. It is recommended when skin testing is precluded by skin disorders or antihistamine use, according to ACP.

The CEAP paper also names several tests that have no value in allergy diagnosis: histamine release, lymphocyte transformation, lymphocyte subsets and cytotoxic testing.

CEAP evaluates nonsurgical medical tests, procedures and therapies, and makes recommendations based on safety, efficacy and cost. Since 1976, CEAP has provided physicians with more than 150 recommendations.

FDA Drug Bulletin

SAFETY OF SILICONE BREAST PROSTHESES

FDA has become increasingly concerned about the possibility of adverse effects from silicone gelfilled breast prostheses and about the long-term risks that these devices may pose.

About 130,000 implant procedures are performed annually in this country, the majority for cosmetic augmentation. Approximately 2 million women in the United States currently have these implants.

Potential Adverse Effects

Previously reported short-term adverse effects include: hardening, discomfort, and pain resulting from fibrous encapsulation of the implant; and breakage of the implant's outer envelope, causing release of the gel. Minute quantities of the gel have been shown to migrate from intact implants. This has raised questions about possible effects on the immune system and fetus.

Study in Rats

More recently, a bioassay study performed by the Dow Corning Corporation, a major manufacturer of silicone gel, demonstrated an excess number of sarcomas in silicone-implanted rats.

The study has been reviewed by an *ad hoc* committee of FDA and National Institute of Health (NIH) scientists

and by FDA's Cancer Assessment Committee. Both groups agreed that the study results are unlikely to be applicable to humans, who are far less responsive to the induction of sarcomas from subcutaneous implantations than are many animal species, including the rat. Both committees concluded that a carcinogenic effect in humans could not be completely ruled out, but that if such an effect did exist, the risk would be very low.

FDA does not believe that there is cause for alarm at present about the safety of gel-filled breast implants, nor is there sufficient justification to remove them from the market at this time. However, there are uncertainties surrounding the possible short-term and long-term adverse effects of these devices. Therefore, as a condition of their continued marketing, the agency will require manufacturers to submit scientific data demonstrating safety and effectiveness of the implants.

To facilitate this process, FDA has convened its General and Plastic Surgery Devices Advisory Panel to obtain advice on the types of information and studies that should be required of manufacturers. Regulations require that FDA give manufacturers a minimum of 30 months to perform the needed studies and submit data.

Other Measures

In the meantime, FDA is undertaking a number of measures to ensure that physicians and patients are adequately informed about possible short-term and long-term problems with breast implants. For example, the agency is reevaluating the labeling required for these devices and, if necessary, will strengthen the warnings and precautions to adequately reflect the most current knowledge about possible adverse effects.

FDA will also consider developing educational materials, either independently or in conjunction with medical organizations, for dissemination to women contemplating breast implants.

The agency will continue to monitor the situation. If information from this ongoing program should point to an unreasonable risk to health, FDA could take regulatory action without waiting for the safety and effectiveness data to be submitted by manufacturers.

RARE COMPLICATION WITH SULINDAC

The labeling of sulindac (Clinoril), a nonsteroidal anti-inflammatory drug (NSAID), has been revised to warn of a rare event, the incorporation of sulindac metabolites into renal calculi.

FDA has received 23 reports of patients being treated with sulindac who developed renal stones consisting of more than 10% sulindac metabolites. The amounts on stone analysis varied from 10% to 90%. (Trace amounts are common with many drugs and are probably of no clinical significance; amounts greater than 10% are characteristic of only a few drugs, such as triamterene, pyridium, and the sulfonamides).

There is a single adverse reaction report of a patient who continued to pass renal stones containing sulindac for 9 months after discontinuing the drug.

In addition, there are two reports of patients with biliary obstruction. At surgery, each patient's common duct contained a "sludge" of crystalline sulindac metabolite.

Symptomatic stone formation due to sulindac appears to be extremely rare. This problem is distinct from the flank pain syndrome related to increased uric acid reported with suprofen (Suprol) in the June 1986, November 1986, and April 1987 *FDA Drug Bulletins*.

Sulindac crystals can form in urine under the conditions of increased metabolite excretion (related to the size of single as well as total daily dose), decreased urine flow, and urinary pH. They have a characteristic "wheat sheaf" appearance. Urine outputs of greater than 240 ml/hour or urinary pH above 5.8 are unlikely to allow crystals, and presumably stones, to form.

Reports Requested

FDA has not received any reports of similar problems with other NSAIDs. The agency would appreciate help from the medical community both in compiling accurate data about sulindac's role in renal or biliary stones and in determining whether other NSAIDs or their metabolites have also been found in stones. Practitioners can help in this effort by reporting any such events to FDA or to the product's manufacturer, who is required to forward the information to FDA.

UPDATE ON *S. ENTERITIDIS* IN SHELLED EGGS

Concern about the continued spread of the problem of *Salmonella enteritidis*-contaminated unbroken Grade A shell eggs leads FDA to recommend that all institutions discontinue use of raw, shelled eggs when using pooled eggs and instead use pasteurized eggs. This is especially important for nursing homes and hospitals as the elderly and immunocompromised are at high risk of serious illness if they eat eggs contaminated with *S. enteritidis*.

The agency wants to emphasize, however, that *S. enteritidis* is not a life-threatening health problem for most healthy individuals.

As discussed in the April 1988 *Drug Bulletin*, the problem initially appeared to be limited to the Northeastern United States. In the last 2 years, although the heaviest incidence continues to be in New England and the Middle Atlantic states, there have been a growing number of sporadic reports from the Southeast, Midwest, and West of cases of *S. enteritidis*. Recent outbreaks traceable to eggs occurred in Virginia, the District of Columbia, Illinois, and Texas. In addition, several foreign countries have reported outbreaks due to eggs from within their own borders.

Although FDA does not feel that the present situation is currently cause for alarm, practitioners should be aware that elderly or immunocompromised patients are at increased risk of developing serious or life-threatening cases of *S. enteritidis*.

According to the Centers for Disease Control (CDC), 24 deaths have been associated with outbreaks in nursing homes or hospitals since January 1985. During 1988, there were four outbreaks in nursing homes or hospitals, with 79 cases, six of them fatal.

Coordinated Effort

FDA is working with local and state health departments, industry representatives, CDC, and the Department of Agriculture to determine the best way to control these outbreaks, which result not from contamination during the cooking or storage processes, but from *S. enteritidis* passed from an infected hen to the egg. FDA and the Department of Agriculture recently cosponsored a public meeting so that all interested groups and individuals could discuss the best measures to take.

Cooking Recommendations

The agencies have made recommendations about ways to cook eggs that can minimize the risk of transmission of *S. enteritidis*. Although the organism is present in the uncracked egg, in most cases thorough cooking will eradicate it or reduce it to levels low enough to be clinically insignificant.

According to research carried out at Cornell University, the following cooking times and temperatures should be adequate to kill *S. enteritidis* (all frying times are for an electric fry pan set at 250°F): Scrambling: one minute. Sunnyside up in an open fry pan: at least seven minutes. Sunnyside up in a covered fry pan: four minutes. Sunnyside over lightly: three minutes on the first side and two minutes on the second. Boiled eggs in shell: seven minutes in boiling water. Poaching: five minutes in boiling water.

In addition, it is recommended that eggs be refrigerated below 45°F and that pasteurized eggs be substituted for fresh eggs in recipes calling for raw or undercooked eggs such as Caesar salad, eggnog, Hollandaise sauce, homemade ice cream or mayonnaise, egg dip, and French toast mix. Blenders, bowls, pans, and mixing utensils used to process raw eggs should be thoroughly cleaned before being used for another purpose. Raw eggs should be cooked immediately after being cracked; they should not be pooled or held in cups or bowls before use.

In responding to patient's questions, practitioners can emphasize that *S. enteritidis* does not appear to pose a life-threatening risk to the general population, but is of particular concern to the elderly and immunocompromised. All patients can, however, be advised to avoid eating raw eggs or products prepared with raw eggs or undercooked eggs. Raw eggs should be contraindicated in the diets of immunocompromised or otherwise debilitated patients.

DRUG APPROVED TO TREAT DIARRHEA OF INTESTINAL CANCER

Octreotide acetate (Sandostatin) has been approved to treat the symptoms of two types of gastroenteropancreatic

(GEP) carcinoma: metastatic carcinoid tumors and vasoactive intestinal peptide (VIP) secreting adenomas.

Octreotide acetate acts in the body in a way similar to the natural hormone somatostatin. In normal subjects, it has the ability to suppress secretion of serotonin and a number of GEP peptides, including vasoactive intestinal peptide and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide acetate can be used to treat the flushing and diarrhea of metastatic carcinoid tumors and the watery diarrhea of VIP-secreting adenomas. With the latter lesion, significant improvement has been noted in the overall condition of patients treated with octreotide who have been unresponsive to other therapies. Improvement in electrolyte abnormalities has often enabled reduction of fluid and electrolyte support.

Present data are insufficient to support the use of octreotide in controlling the size, rate of growth, or metastases in patients with (GEP) tumors, or its safety and efficacy in other GEP-endocrine-secreting tumors.

The recommended route of administration is subcutaneous injection, which can be administered by the patients themselves or by the care-giver at home. Multiple injections at the same site within a short period should be avoided. Under emergency conditions, intravenous bolus injections have been used.

Gallbladder Monitoring

Patients being treated with octreotide should be monitored periodically for gallbladder disease. Surgical intervention has been required in a few patients who, while on octreotide therapy, developed severe abdominal pain associated with cholelithiasis.

It is recommended that patients on extended therapy be evaluated periodically with ultrasound imaging of the gallbladder and bile ducts.

Drug Interactions

Although patients receiving other drugs to control the symptomatology or progression of the disease have generally not shown signs of serious drug interaction, close monitoring is necessary for patients with severe symptoms who receive octreotide in addition to other therapies used to control glycemic states (e.g., sulfonylureas, insulin, diazoxide) or to beta blockers or agents for the control of fluid or electrolyte balance. Adjustment in the dosages of these drugs should be made as the symptoms of the disease are brought under control.

Because octreotide has been associated with alteration in nutrient absorption, its effect on the absorption of any orally administered drug should be carefully considered. FDA is aware of one transplant rejection episode (renal/whole pancreas) in a patient immunosuppressed with cyclosporine. In this patient, octreotide treatment to reduce exocrine secretion and close a fistula resulted in decreases in blood levels of cyclosporine and may have contributed to the episode.



AMERICAN ACADEMY OF PEDIATRICS

SEX EDUCATION IN SCHOOLS: DOES IT WORK?

Sex education in school in and of itself appears to have little or no effect on altering sexual activity, promoting contraception use or lowering teen pregnancy, according to a critical review of five past studies.

"Existing data suggest that a classroom course alone cannot be expected to change sexual behavior in a direction that is in opposition to the adolescent's sexual world as molded by the television, motion picture, music and advertising industries, as well as peer group and adult role models," according to James W. Stout, M.D., and Frederick P. Rivara, M.D., MPH, authors of the review.

Published in the March issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), the review examined the results of five previous studies in which the effect of junior and senior high school sex education programs on teen sexual activity, contraceptive behavior and pregnancy rate were evaluated. The studies represented a wide variety of diverse geographic locations, as well as racial and socioeconomic groups.

The authors, from Harborview Medical Center, the University of Washington and Children's Hospital and Medical Center, Seattle, concluded: "To place the burden of counteracting the prevailing forces in our society toward premarital sex on our schools alone is both naive and inappropriate."

One problem, said the authors, is that we may be asking these programs—and our schools—to accomplish too much. "A multifactorial problem such as adolescent pregnancy demands a multifactorial solution," they noted.

The authors reported on a comprehensive community-wide sex education program in which parents, teachers, ministers, community leaders and the media were involved in a joint effort to postpone the age of teens' first sexual experience, promote the use of consistent contraception and lower the teen pregnancy rate. Sex education in the schools was only a small part of the overall effort. Two and three years after the program was initiated, the teen pregnancy rate declined by an estimated 35 percent.

Another multifaceted approach to the problems related to teen sexuality discussed by the authors is the services provided by the increasingly popular alternative of school-based health clinics, a concept endorsed by the AAP. However, they noted that these clinics should be viewed with caution until studies evaluating their effectiveness have been performed.

The authors pointed out the fact that the five studies

they reviewed did have some design limitations. For example, there was no uniformity in the school programs and therefore no control of the content, length, or quality of the programs. Also, the studies were retrospective and suffer from the possibility of differential recall bias.

Nevertheless, they concluded: "The expectations of altered adolescent sexual activity, contraceptive behavior, and pregnancy are unlikely to be fulfilled by these programs, and we suggest that the effort to fight for sex education on these terms is not justified unless an effect is shown in further studies."

AAP RELEASES CIRCUMCISION STATEMENT

The American Academy of Pediatrics (AAP) has released its statement on circumcision, concluding that the procedure has potential medical benefits and advantages, as well as inherent disadvantages and risks.

According to AAP president Donald Schiff, M.D., the Academy is recommending that the decision is one best made by parents in consultation with their physician.

"In addition to the medical aspects, other factors will affect the parents' decisions, including esthetics, religion, cultural attitudes, social pressures, and tradition," the AAP statement says.

Physicians should explain and discuss the benefits and risks of circumcision with parents, and informed consent should be obtained before the procedure is performed. Most male infant born in this country are circumcised in the newborn period, although the circumcision rate appears to be falling.

Since 1971, the AAP has maintained the position that there was no absolute medical indication for routine circumcision of the newborn. New information has recently appeared in the literature suggesting possible medical benefits from newborn circumcision. Summarized below are the main points of the AAP's new statement on circumcision, addressing the new evidence:

Urinary Tract Infections

Studies conducted at U.S. Army hospitals in 1985 involving more than 200,000 males showed a greater than tenfold increase in urinary tract infections in uncircumcised as compared with circumcised male infants; moreover, as the rate of circumcision declined over the years, the incidence of urinary tract infection increased.

However, the AAP statement says: "It should be noted that these studies in Army hospitals are retrospective in design and may have methodologic flaws. For example, they do not include all boys born in any single cohort or those treated as outpatients, so the study population may have been influenced by selection bias."

Circumcision "may result in a decreased incidence of urinary tract infection. However, in the absence of well-designed prospective studies, conclusions regarding the relationship of urinary tract infection to circumcision are tentative," according to the statement.

Cancer of the Penis

Circumcision has been shown to decrease the incidence

of cancer of the penis (a rare condition) among U.S. males. This condition occurs almost exclusively in uncircumcised men. Poor hygiene, lack of circumcision, and certain sexually transmitted diseases all correlate with the incidence of penile carcinoma.

The decision not to circumcise a male infant must be accompanied by a lifetime commitment to genital hygiene to minimize the risk of developing penile cancer.

Sexually Transmitted Diseases

"Evidence regarding the relationship of circumcision to sexually transmitted diseases is conflicting," the AAP statement says. "Although published reports suggest that chancroid, syphilis, human papillomavirus and herpes simplex virus type 2 infection are more frequent in uncircumcised men, methodologic problems render these reports inconclusive."

Cervical Cancer

Evidence linking uncircumcised men to cervical carcinoma is also inconclusive, the statement notes. However, an increased incidence of cancer of the cervix has been found in sexual partners of uncircumcised men infected with human papillomavirus.

The strongest predisposing factors in cervical cancer are a history of intercourse at an early age and multiple sex partners.

Pain and Behavioral Changes

Infants undergoing circumcision without anesthesia demonstrate physiologic responses suggesting that they are experiencing pain. Behavioral changes include a cry pattern indicating distress during the circumcision procedure and changes in activity (irritability, varying sleep patterns) and in infant-maternal interaction for the first few hours after circumcision. "These behavioral changes are transient and disappear within hours after surgery," the statement notes.

Local Anesthesia

Dorsal penile nerve block in appropriate doses may reduce the pain and stress of newborn circumcision. "However," according to the statement, "reported experience with local anesthesia in newborn circumcision is limited, and the procedure is not without risk."

Complications due to local anesthesia are rare and consist mainly of hematomas and local skin necrosis. "It would be prudent to obtain more data from large controlled series before advocating local anesthesia as an integral part of newborn circumcision," the statement says.

Complications, Contraindications, Hygiene, Infections

The exact incidence of postoperative complications is unknown, but large series indicate that the rate is low, approximately 0.2 to 0.6 percent. The most common complications are local infection and bleeding.

Circumcision should only be performed on stable, healthy infants. It is contraindicated in an unstable or sick infant. It is prudent to wait until a premature infant

meets criteria for discharge before performing circumcision.

Circumcision prevents phimosis (inability to retract the foreskin), paraphimosis (accumulation of fluid and swelling of the prepuce and glans), and balanoposthitis (inflammation of the prepuce and glans). It is particularly important that uncircumcised boys be taught careful penile cleansing, the AAP statement notes.

POST-TRAUMATIC STRESS DISORDER: INCREASINGLY COMMON IN CHILDREN

After a traumatic shock, whether it be a dog bite or a school shooting, it has become increasingly common for children to suffer from post traumatic stress disorder. Unfortunately, says an expert, the condition often goes undiagnosed.

Post-traumatic stress disorder can be the result of single-blow, external shocks —such as dog bites, rapes or school shootings— or multiblow, longstanding external stress —such as incest, child abuse and war, said Lenore C. Terr, M.D., Professor of Psychiatry, University of California, San Diego.

Speaking at the American Academy of Pediatrics' (AAP) Spring Session, Dr. Terr said that since the diagnosis is fairly new to medicine, many physicians are not yet acquainted with all the signs and symptoms of psychic trauma in children.

According to Dr. Terr, signs and symptoms of the stress disorder are grouped into three areas: a change in cognitive skills and perception; fears; and repetitive behavior.

Dr. Terr said teachers and the news media can be tremendously effective in helping prevent post-traumatic stress disorder in children. They can do this by anticipating and explaining the kind of feelings that may be stirred up after a local or national tragedy and by immediately presenting experts to discuss the event.

"There are some differences between the traumatic conditions induced by single versus multiple shocks," Dr. Terr said. "When shocks are longstanding, memory becomes impaired, emotional expression becomes limited and character changes are massive. When shocks are short, memory is clear, emotions are intense and omens develop."

Furthermore, since children convey their post-traumatic experiences —ghost sightings, stories, behavioral reenactments— to other children, traumatic stress is contagious, Dr. Terr said.

Children can also experience the disorder vicariously. "One or two isolated symptoms will develop following suicides or illnesses among peers or after national tragedies," Dr. Terr said.

Treatments for the stress disorder include family therapy, group therapy, individual play therapy, intensive psychotherapy and medications, Dr. Terr said.

CHILDREN'S DEPRESSION ON THE RISE

Depression is a problem faced by an increasing number of children and adolescents at increasingly younger ages.

The illness, however, can be difficult to diagnose in young people because it can masquerade as a behavior problem.

"Studies conducted over the past 50 years show the onset of depressive illness is occurring earlier and earlier," noted John C. Pomeroy, M.D., while speaking at the American Academy of Pediatrics' (AAP) Spring Session. "While the complexities of diagnosing the illness raise some disputes in just how early it can occur, severe depression has been found in children as young as six."

Dr. Pomeroy, Assistant Professor of Psychiatry at State University of New York, Stony Brook, said one problem in diagnosing depressed children is that doctors sometimes see the symptoms —such as lack of concentration and deterioration in school performance— as signs of a behavior problem.

"While a depressed child and a child with a conduct problem may behave in a similar manner," he explained, "there are certain signs that should lead parents and doctors to suspect depression as the cause: withdrawal from friends and family, changes in sleeping and eating habits, comments about hopelessness and any other sudden change in behavior."

According to Dr. Pomeroy, there are a number of causes of depression in children and adolescents, including biologic abnormalities, family history and negative social factors such as an abusive home situation or separated parents. Puberty also seems to have an influence as there is a rapid increase in severe depression —particularly manic-depressive illnesses— after its onset.

"The key to treating depressed children is putting them in a more nurturing setting," he said. "For some, particularly those with psychosocial problems, that means counseling and school and/or family intervention. Others respond well to medication. It's something that must be judged on a situation by situation basis."

Dr. Pomeroy also pointed out that, while the classic symptoms of depression are the same for adults and children, subtle differences exist based on the child's age and the degree to which he can express himself. For example, young depressed children will tend to look sad, show decreased self-esteem and complain of physical ailments.

"Another difference between depressed adults and depressed children," said Dr. Pomeroy, "is that the children have more hallucinations, which often take the form of voices saying bad things about the child."



SMOKING, PASSIVE SMOKE EXPOSURE BOTH BOOST CERVICAL CANCER RISK

Cigarette smoking and exposure to passive smoke both appear to increase a woman's risk of developing cervical cancer, a study in the *Journal of the American Medical Association* indicates.

Current smokers run 3.4 times the risk of non-smokers of developing cervical cancer, concludes the population-based, case-control study conducted by Martha L. Slattery, PhD, MPH, of the University of Utah School of Medicine, Salt Lake City, and colleagues. Having smoked for five or more "pack-years" raised the risk nearly three times, while women who smoked at least 100 cigarettes during their lifetimes more than doubled their cancer chances.

Women who reported that they were exposed to passive smoke for three or more hours per day were nearly three times more likely to have cervical cancer than those not exposed to passive smoke, the authors report. The increased risk from passive smoke exposure was "independent of the risks associated with personal cigarette smoking, educational level, church attendance, age, and number of sexual partners, although the greatest risk was in women were non-smokers (a nearly three-and-a-half-fold greater risk)," the authors say.

"The risk associated with passive smoking in this study is as strong as that observed from personal cigarette smoking," the authors say. "The greatest risk associated with passive smoking is that inhaled in the home, possibly because people exposed to smoke at home incur larger doses of exposure either from being in a more confined area or having a more constant exposure."

In smokers, the greatest risk of cervical cancer was seen among women less than 30 years of age and in women who have had one or no sexual partners, say the authors. "This is probably because cigarette smoking will be a greater risk factor in women who do not have other major competing risk factors," they write.

The study results support previous research indicating that women smoke cigarettes are at increased risk of

developing cervical cancer, the authors note. However, they add, one of their study's strengths is that many of the subjects belong to the Church of Jesus Christ of Latter-day Saints (Mormons), which proscribes tobacco use. As a result, they say, a large segment of the study population did not smoke cigarettes, so "we were able to assess passive smoking risk in non-smokers as well as smokers. We evaluated several indicators of exposure to passive smoke and found that, regardless of the indicator used, the results were consistent."

The mechanisms by which smoking may increase the risk of cervical cancer link are beginning to be evaluated, the authors note. "Recent studies have shown that constituents from cigarette smoke can be transmitted through the blood to distant tissues and organs, and these substances have been detected in the uterine cervix of cigarette smokers," they write. The exact mechanism that may be involved remains unclear, however.

In an accompanying editorial, Peter M. Layde, MD, MSc, of the Marshfield Medical Research Foundation, Marshfield, Wis., notes that while this study adds to the evidence of a smoking/cervical link, cause-and-effect remains to be shown. He raises some minor concerns about methodology—especially in measuring passive smoking exposure—and notes that since this is "the first adequate epidemiologic evaluation of the role of passive smoking in causing cervical cancer... the findings should be interpreted cautiously." But, he notes, "definitive resolution of this issue is not urgent from the standpoint of public health or preventive medicine. It is clear that women should quit smoking cigarettes for many reasons other than a possible increased risk of cervical cancer.

"Considerable evidence has also been accumulating recently that passive smoke exposure to smoke of other people's cigarettes is harmful to both children and adults; moreover, cigarette smoke is irritating to many individuals," Layde adds. "Unfortunately, the continuing importance of passive exposure to cigarette smoke in the home makes the ideal occurrence unlikely that the issue of passive smoking might be of only historical interest before its role in cervical carcinogenesis is totally clarified."

JAMA March 17, 1989

AUTOPSY STUDIES PROVIDE BETTER UNDERSTANDING OF DIAGNOSTIC FALLIBILITY

An analysis of autopsy findings over the past 50 years shows little change in the accuracy of clinical diagnoses for 11 common diseases—at least among patients who underwent autopsies, says a report in the *Journal of the American Medical Association*.

The authors, Robert E. Anderson, MD, of the University of New Mexico School of Medicine, Albu-

querque, and colleagues, examined published studies encompassing more than 50,000 autopsies in Europe and the United States to determine the accuracy of the clinical diagnoses for these diseases in persons dying during the period 1930 through 1977. They also wanted to test the hypothesis that "there is an irreducible error rate inherent in the diagnostic process, at least among persons dying in the hospital on whom an autopsy is performed."

The authors found that the accuracy of clinical diagnoses during this period appeared to improve for some of the diseases studied (rheumatic heart disease and leukemia); worsened for others (pulmonary tuberculosis, peritonitis, lung cancer, liver cancer, and stomach cancer), and remained unchanged for a significant number (pulmonary embolism, primary cirrhosis of the liver, gastric/peptic ulcer, and acute coronary thrombosis/myocardial infarction).

These diseases were chosen because they are relatively common and because they have unambiguous physical characteristics. The authors considered only cases where the disease was either the underlying cause of death or had contributed significantly to the patient's demise.

The authors say their findings apply only to a highly restricted group of patient—those who die and are autopsied, not those who recover. Also, the data came from different patient populations in different countries at institutions that may have had different autopsy rates and policies. "Despite these limitations, there can be little question that a significant proportion of persons dying of, or suspected of dying of, the 11 entities we evaluated were misdiagnosed," they conclude.

Although the causes of inaccurate diagnosis are complex and not well understood, some studies suggest physician error is responsible for a majority of diagnostic discrepancies, they write. Therefore, it is "perhaps not surprising that improvements in diagnostic technology have not had an apparent impact on the accuracy of clinical diagnostics among persons coming to autopsy."

In fact, diagnostic accuracy may be adversely affected by overreliance on diagnostic testing, the authors say. This does not imply that new technologies are not important. "However, among people who die and are autopsied, their impact is not as apparent as might be anticipated, and there is no evidence among these studies to support the notion that modern technology has obviated the need for autopsy verification," they write.

"In today's litigious climate, few physicians are eager to have their errors or failures laid bare or publicized. Yet for performance to improve, the nature and causes of the failures must be studied for clues that can help in the future. We believe that elucidation of the circumstances and events that lead to discrepant diagnoses will... confirm the presence of an irreducible necessary fallibility, emanating from the uncertainties inherent in medical predictions based on human observation and the laws of natural science." Recognition of this "unavoidable baseline level of error" is crucial for understanding medical fallibility and could help blunt present litigious excesses, they add.

The findings suggest "a new way in which the autopsy can be used to monitor clinical diagnostics to identify possible sources of systematic weaknesses and provide

data that can be used to approach the difficult subject of necessary fallibility," they conclude, saying studies such as this will lead to the discovery of "systematic faults in the medical diagnostic process that can be corrected. While improvement in performance through learning is highly desirable... society must come to understand and accept a realistic degree of necessary fallibility."

JAMA March 17, 1989

PUBLIC HEALTH STRATEGIES FOR CONFRONTING AIDS

A report in the *Journal of the American Medical Association* offers a state-by-state rundown on AIDS-related legislative and regulatory policy in the United States, and says the review "reveals a mixed record". Most states have come to accept research showing "the sometimes remarkable efficacy of well-targeted education and counseling and the promise of pharmaceutical research," says author Larry O. Gostin, JD, of the American Society of Law and Medicine and the Harvard School of Public Health, Boston. "So too has there been wide acceptance of the critical public health importance of confidentiality and guarantees of antidiscrimination," he says. However, the author adds, many state legislatures "also have been highly susceptible to the attitude that the primary modes of (human immunodeficiency virus) transmission are immoral, even criminal." What's more, "political pressures on legislators to use the coercive powers of the state to combat the epidemic are unmistakable," he writes. "Often, these compulsory interventions focus on low-risk groups (eg, premarital screening) and behaviors (eg, spitting, biting, or donating blood), revealing that they are motivated as much by political and moral concerns as by epidemiological data. The use of coercive powers, far from accomplishing the ostensible of impeding the AIDS epidemic, could well fuel it."

JAMA March 17, 1989

ANESTHESIA LIABILITY

In anesthesia-related malpractice claims, the "standard of care" rendered to a patient significantly influences the likelihood and amount of a liability award, a study in the *Journal of the American Medical Association* indicates. However, says the study by Frederick W. Cheney, MD, of the University of Washington School of Medicine, Seattle, and colleagues, even if an anesthesiologist provides what is considered to be appropriate care, there is still a significant chance that a malpractice claim will pay off. The authors base their conclusion on an analysis of more than 1,000 malpractice claims filed for alleged anesthesia-related patient injuries. The "standard of care" in these cases was judged by a practicing group of anesthesiolo-

gists. "We found that payment was made in more than 80 percent of claims made by patients who were judged to have received substandard anesthetic care," the authors report. But payment also was made in more than 40 percent of claims when the anesthesia care was judged to be the appropriate, they add. "We conclude that the tort-based system of patient compensation for injury clearly favors payment to the injured patient, but inequities exist for both patient and physician."

JAMA March 17, 1989

AGE OF ALCOHOLISM ONSET

Alcoholics whose alcohol abuse starts early in life may have a deficit in the neurotransmitter serotonin, the chemical messenger believed to help regulate mood, aggression and impulses, two reports in March's *Archives of General Psychiatry* suggest. The studies by Laure Buydens-Branchey, MD, of the Veterans Administration Medical Center, Bronx, NY, and colleagues involved male alcoholics aged 25 to 60. The first study found patients who began abusing alcohol before age 20 were twice as likely to have been jailed for violent crimes, three times as likely to have attempted suicide as those whose alcoholism began later in life. All of these mood and aggression control problems are believed influenced by serotonin. Early-onset alcoholics also had a significantly higher incidence of paternal alcoholism. The second study analyzed patient blood samples for a gauge of serotonin function—the ratio of serotonin's chemical precursor, tryptophan, to other amino acids. An association

between a low tryptophan ratio and depressive and aggressive tendencies was significant only in patients who began abusing alcohol as teenagers. "Theoretically, individuals in whom a serotonergic deficit is suspected should respond to tryptophan supplementation or to treatment with other agents modifying serotonin functional levels. This could affect their level of alcohol consumption as well as their depressive or hostile tendencies," the study says.

NEUTRON THERAPY FOR STUBBORN TUMORS

External radiation using high-energy fast neutron beams can often be effective in treating certain locally advanced tumors that cannot be removed surgically and are considered resistant to conventional radiation therapy, says a report in the March *Archives of Surgery*. The report, by Lionel Cohen, MD, and Frank R. Hendrickson, MD, of the Fermi National Accelerator Laboratory (Fermilab), Batavia, Ill., says local long-term control has been achieved using neutron therapy in a wide range of cancerous tumors. "Complete response and long-term remission, with local control rates between 50 percent and 70 percent," have been reported in some cases, the authors say. "Though neutron beam therapy is clearly not a panacea for all advanced cancer, there does appear to be a distinct subset of patients who can benefit substantially from this treatment," the researchers say. "Neutrons are probably indicated in most locally advanced, non-resectable tumors that are classified histologically as radioresistant."



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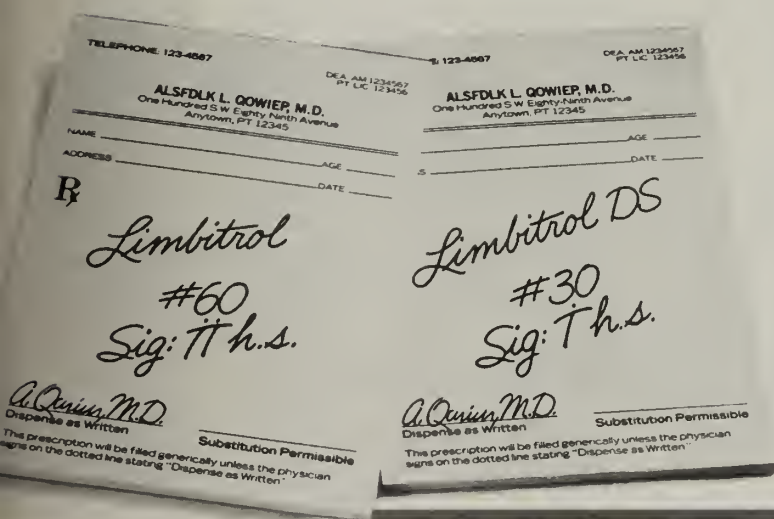
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Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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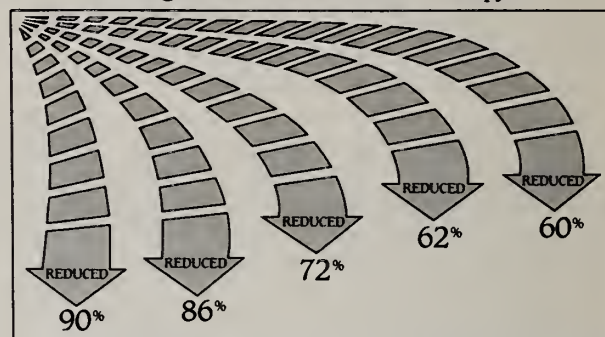
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VOL. 81 / NUM. 6

JUNIO 1989



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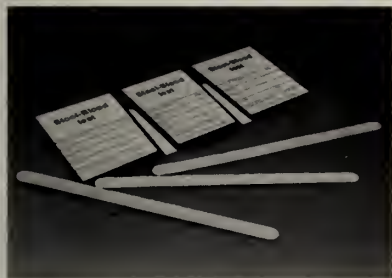
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50,000 people will be saved from colorectal cancer this year. You can save one.

Save yourself! Colorectal cancer is the second leading cause of cancer deaths after lung cancer. More than 90% of colorectal cancers occur equally in men and women past age 50. Early detection provides the best hope of cure. That's why if you're over 50, you should take this simple, easy slide test of your stool every year. This Stool Blood Test kit is chemically treated to detect hidden blood in the stool and can be done at the time of your periodic health examination so your doctor will know the results.



The presence of hidden blood usually indicates some problem in the stomach or bowel, not necessarily cancer. Positive tests must be followed by further testing to find out what the problem is.

Other tests for colorectal cancer you should talk to your doctor about: digital rectal exam (after age 40); the procto test (after age 50). It is important to report any personal or family history of intestinal polyps or ulcerative colitis, and any change in your bowel habits, which could be a cancer warning signal.

The American Cancer Society wants you to know.



Nuestra Portada

Escuela de Medicina Tropical. Acuarela de una de las fachadas del edificio donde primero estuvieron ubicadas las facultades de Medicina y de Odontología de la Universidad de Puerto Rico, obra del Dr. Servando Pico. El autor es natural de Santurce Puerto Rico y desde pequeño comenzó sus estudios de pintura con el maestro Guillermo Sureda. Una vez en la Universidad de Puerto Rico estudió pintura, historia, apreciación del arte así como dibujo y composición.

Sus acuarelas nos muestran en su mayoría temas de nuestro Viejo San Juan, aunque se considera gran parte de su obra de índole costumbrista. El autor ha participado en certámenes de acuarela en Puerto Rico y el exterior incluyendo Estados Unidos, Alemania y España. El Dr. Pico es graduado de la Escuela de Odontología de la Universidad de Puerto Rico y ejerce su profesión en el área de Guaynabo, compartiendo su práctica de Odontología con su gran afición por la pintura, particularmente la acuarela.

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico otra vez agradece al Dr. Pico su colaboración, al permitir la reproducción de una de sus obras en nuestra portada.

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DERMATOLOGY DIAGNOSIS

María R. Picó Moreno, MD
Alma Cruz, MD
Jorge L. Sánchez, MD

This is an 11 year-old girl referred to our clinics, who at age 2 sustained trauma to her right foot with fractures of several toes. Several weeks later, she developed swelling, and an ulcerated plaque on the lateral side of the foot. Bacterial cultures at that time were negative, and the lesion healed after 5 months with conservative treatment. Six months later, a plaque with multiple draining sinuses appeared on the medial aspect of the right ankle. After three months, this lesion was partially healing when another one appeared on the left infraorbital area. Multiple systemic medications and topical treatment were given, but the lesions continued to appear, each time showing slow healing and more deformities. At age 8, she was bedridden due to gradual and severe contractures. Family history was negative for tuberculosis.

Physical examination revealed a bedridden cachectic girl with multiple depressed and deformed scars on the legs and forearms. There were erythematous tender plaques with multiple draining sinuses on the left foot and medial aspect of right ankle. On the right hand, there was an erythematous nodule, and on the left infraorbital area there was an erythematous ulcerated plaque with crust. There were small cervical lymphadenopathies, but the rest of the examination was negative.

The X-rays of the affected limbs showed lytic lesions and a moderate periosteal reaction on the phalanges of toes and epiphyses of the femur and right tibia. Chest x-rays were negative for pulmonary disease. Gallium and bone scans reported increased tracer concentrations in the proximal and distal aspects of long bones.

Complete blood count showed leukocytosis and hypochromic microcytic anemia. Cultures from blood, urine, cerebrospinal fluid, bone marrow, lymph node and skin were negative for bacteria, fungi and acid fast bacilli (AFB). Gastric aspirate and sputum were also negative for AFB. Bone marrow aspirate was reported reactive with megaloblastic changes and increased plasma cells. Lymph node biopsy showed chronic lymphadenitis. The tuberculin test was 15mm in diameter after 48 hours.



WHAT IS YOUR DIAGNOSIS?

- A) Sporotrichosis
- B) Scrofuloderma
- C) Metastatic tuberculous abscesses
- D) Atypical mycobacterial infection
- E) Mycetoma (madura foot)

Diagnosis: Atypical Mycobacterial Infection

This patient was started empirically on isoniazid and rifampin due to the positive PPD. In spite of this treatment, she continued to develop new lesions. Fresh skin tissue was again sent for culture and was reported as *Mycobacterium avium* complex, with resistance to all antituberculous drugs. Tetracycline and erythromycin were added to the above therapy, but the disease continued progressing until death at 11 years of age.

The atypical mycobacteria are a group of microorganisms which include facultative human pathogenic and non-pathogenic species. They are acid fast, alcohol fast, aerobic, and non-motile bacilli. They are widely distributed in nature, and rather than being transmitted person-to-person, as *M. tuberculosis*, they are acquired from the environment. They are so ubiquitous that skin tests with antigens from various strains have shown that many people have been sensitized by some of these organisms.¹ In addition, with the relative decrease in the incidence of tuberculosis, there has been a relative increase in the incidence of atypical mycobacterial infections in some regions.² The advent of immunosuppressive therapies and the acquired immune deficiency syndrome (AIDS), has caused these organisms to be described more frequently.

Infections due to the atypical mycobacteria are more commonly described to involve lungs, lymph nodes, skin, and the skeletal and genitourinary systems, as well as disseminated infection. The most common pathogen in the USA is *M. avium-intracellulare* (MAI), while in Great Britain it is *M. kansasii*.² The lung is the organ most frequently affected and the clinical presentation is similar to that of tuberculosis. The most common pathogens in pulmonary disease are MAI, *M. kansasii* and *M. xenopi*, though others such as *M. scrofulaceum*, *M. chelonae*, *M. szulgai*, and *M. malmoense* are implicated less frequently.²

Some atypical mycobacteria are well known for their characteristic presentation. *M. marinum* causes warty skin lesions secondary to trauma associated with fresh and salt water, so that names such as "swimming pool granuloma" and "fish tank granuloma" are used to describe these lesions.³ *M. marinum* is the most common pathogen in mycobacterial soft tissue infection.⁴ Usually, the lesion is solitary, but a sporotrichoid pattern has been described.⁵

M. ulcerans is characterized as causing dermal necrosis producing a painless, deeply undermined ulcer. Inoculation is probably through microtrauma. A toxin produced by this organism is the suspected cause of the necrosis.⁶ The differential diagnosis of this lesions must include blastomycosis, pyoderma gangrenosum and necrotizing cellulitis.⁷

M. chelonae and *M. fortuitum* are the only rapid-growing mycobacteria pathogenic to man. They have been reported to contaminate injection solutions (cold postinfection abscesses).⁸ Abdominal infections have been reported after penetrating wounds and surgery.⁹ In the normal host, infections usually remain localized. However, disseminated disease has occurred in immunosuppressed patients.⁷ A sporotrichoid pattern of skin infection has also been reported.¹⁰

M. scrofulaceum is most commonly associated with cervical lymphadenitis in young children, involving mostly submandibular and submaxillary nodes, unilaterally, without constitutional symptoms nor other organ involvement.⁷

M. kansasii has more varied presentations. It is mostly a lung pathogen but it may cause skin infection, cervical lymphadenopathy, joint disease and disseminated infection.⁴ Skin infection occurs after trauma and may manifest as sporotrichoid or granulomatous lesions.¹²

Infections by MAI generally involve the reticuloendothelial system, lung, bone or skin.¹³ MAI and *M. kansasii* are the most frequent atypical mycobacteria associated with disseminated infection, though all other groups of these organisms have been described to cause disseminated disease. Immunosuppression is an important predisposing factor for dissemination, but it is by no means a requirement.^{13, 14} Primary skin disease due to MAI is rare, and its manifestations are variable including generalized cutaneous ulcerations or granulomas, pustular lesions and soft tissue swellings.⁷

Culture identification is important for diagnosis of infection by atypical mycobacteria, since tissue staining for acid fast bacilli is often negative.^{13, 14} and the variable histologic presentation does not correlate with infection by a specific species of mycobacteria.¹⁵ The clinician is forced to rely on the competence of the microbiologist in identifying the organism. This is complicated by the fact that environmental contamination is a possibility in a positive culture, and that some very common contaminating mycobacteria are very similar to pathogenic ones.


Regarding therapy, identification of the causative organism is crucial since response to drug therapy varies from species to species. *M. kansasii* is the most likely to respond to antituberculosis drugs.⁷ *M. marinum* and *M. xenopi* are also relatively drug sensitive, but *M. avium* complex, *M. scrofulaceum* and *M. fortuitum* are rather resistant.⁴ Surgery may be indicated when the infection is localized. Multiple drug combinations of antituberculous drugs are the usual therapy, but success with erythromycin, aminoglycosides, tetracyclines, sulfas, clofazimine, ansamycin and threnamycin have been reported.

In summary, this case presentation points to the importance of including the atypical mycobacteria in the differential diagnosis of primary cutaneous inoculation infections. It also demonstrates the difficulty the clinician may face in establishing the diagnosis and starting adequate therapy in atypical mycobacterial infections.

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CLINICAL STUDIES

Hyperprolactinemia and Its Management

Juan R. Otero, MD
Francis Baco, MD
Francisco Aguiló, MD, FACP

The advent of radioimmunoassay (RIA) techniques for measuring serum prolactin levels and the widespread availability of computerized tomography (CT) during the last decade have contributed to a higher recognition of patients diagnosed as hyperprolactinemic or possibly harboring a micro-or macroprolactinoma.

More recently, the use of the dopamine agonist, bromocriptine mesylate, has radically altered the treatment of these patients who were previously mostly treated surgically, especially those with macroadenomas and visual field impairments.

Our present study analyzes the therapeutic response of hyperprolactinemic patients seen at the University Hospital to bromocriptine versus neurosurgical therapy, and compares our experience with that reported in the current medical literature.

Subjects and Methods

Forty five patients with hyperprolactinemia were studied. Information was obtained by reviewing the medical records (1974 to 1986) of the Endocrinology Division of the University Hospital. Relevant data comprised initial and follow-up endocrine and neurological findings, prolactin levels and head CT results prior to and during bromocriptine therapy, and prolactin levels before and after surgery.

Sixteen patients underwent neurosurgery: 11 transphenoidal hypophysectomies and 5 craniotomies.

Serum prolactin was measured by conventional RIA (NV = 2.3 to 17 ng/dl). Depending on initial positive head CT scan findings, patients were classified as either micro or macroprolactinoma; "negative" were those not showing any tumor.

Response to bromocriptine therapy was classified as "complete" or "partial". Complete response was defined as both, a decrease in serum prolactin to normal values and improvement of neurologic and endocrine symptoms. A partial response occurred when the prolactin levels or the clinical symptoms improved but were not corrected.

Results

The patient profile is shown in Table 1. It comprised 35 females and 10 males with a mean age of 29 and 35 years, respectively. The mean initial prolactin values were twice as high among males than in females, namely, 1427 ± 508 vs. 743 ± 194 ng/ml, respectively.

Headache was the most frequent neurological symptom present at initial evaluation in both females and males (62%), while visual impairment was reported by 42% of the patient population (Table 2).

Table 1

Profile of Hyperprolactinemic/Prolactinoma Patients		
	Mean age (years)	Mean initial Prolactin values (ng/ml)
Females n=35	29 ± 1.6	743 ± 194
Males n=10	35 ± 4.8	$1,427 \pm 508$
Total n=45	32 ± 3.2	$1,085 \pm 351$

Table 2

Neurological Symptoms in Hyperprolactinemic Patients		
	Headaches (%)	Decreased vision (%)
Females n=35	21 (60)	14 (40)
Males n=10	7 (70)	5 (50)
Total	28 (62)	19 (42)

Endocrinological symptoms (Table 3) comprised amenorrhea and/or galactorrhea in 80% of females and impotence and/or loss of libido in 70% of males. Loss of libido per se was relatively uncommon among females. Forty percent of the male population had galactorrhea.

As shown in Table 4, the initial head CT scan revealed a macroprolactinoma in 16 (36%) a microprolactinoma in 15 (33%), and in 14 (31%) no adenoma was found. It is noteworthy that 80% of the studied males had a macroprolactinoma in keeping with significantly higher pro-

lactin levels in this group (mean initial prolactin values 10-fold higher than those of microprolactinoma group and almost 30 times the values of those without tumor).

Table 3

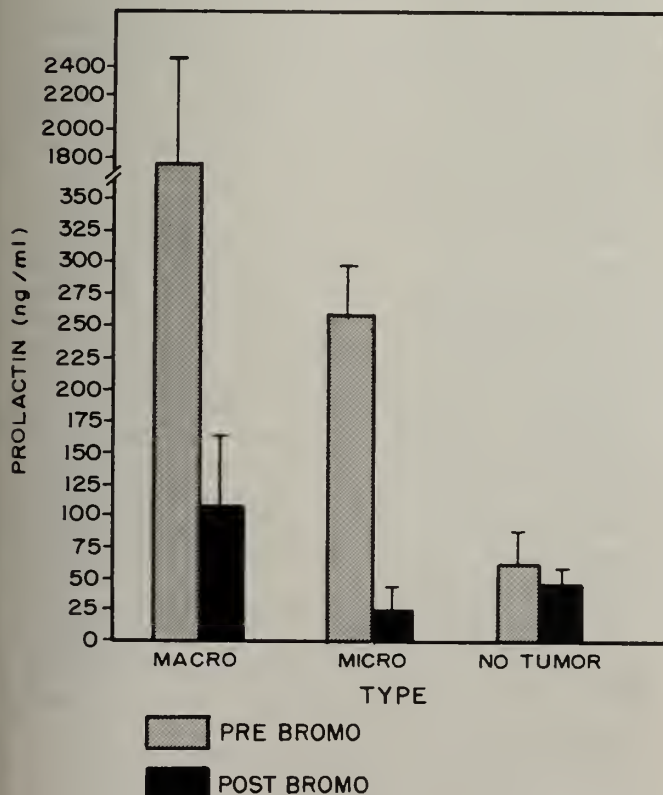
Endocrinological Symptoms in Hyperprolactinemic Patients		
	Amenorrhea and/or Galactorrhea (%)	Impotence and/or Loss of libido (%)
Females n=35	28 (80)	4 (11)
Males n=10	4 (40)	7 (70)
Total	32 (71)	11 (24)

*Table 4

Baseline Prolactin Values in Relation to Initial Diagnosis by Head CT Scan		
Diagnosis	Number of patients (%)	Mean Prolactin (ng/ml.)
MACRO	16 (36)	1,824.9 \pm 457
MICRO	15 (33)	246.2 \pm 44
NO TUMOR	14 (31)	62.8 \pm 14.5

Figure 1 shows the mean serum prolactin before and during therapy with bromocriptine in the 3 groups. In the macroprolactinoma group there was almost a 20 fold

FIGURE 1. PROLACTIN LEVELS PRE AND DURING THERAPY WITH BROMOCRIPTINE



decrease in prolactin (1719 \pm 440 vs. 101 \pm 59 ng/ml), whereas in the micro group prolactin decreased to normal levels (253 \pm 23 vs. 9.3 ng/ml). The fall in serum prolactin in the no tumor group was much less impressive (62.8 \pm 14.5 vs. 46.4 \pm 19.4 ng/ml).

Figure 2 exemplifies the dramatic response obtained with bromocriptine treatment in one of our patients with a macroprolactinoma. The initial head CT scan showed a big tumor with suprasellar extension. Complete resolution of the mass was achieved 4 months after starting bromocriptine therapy.

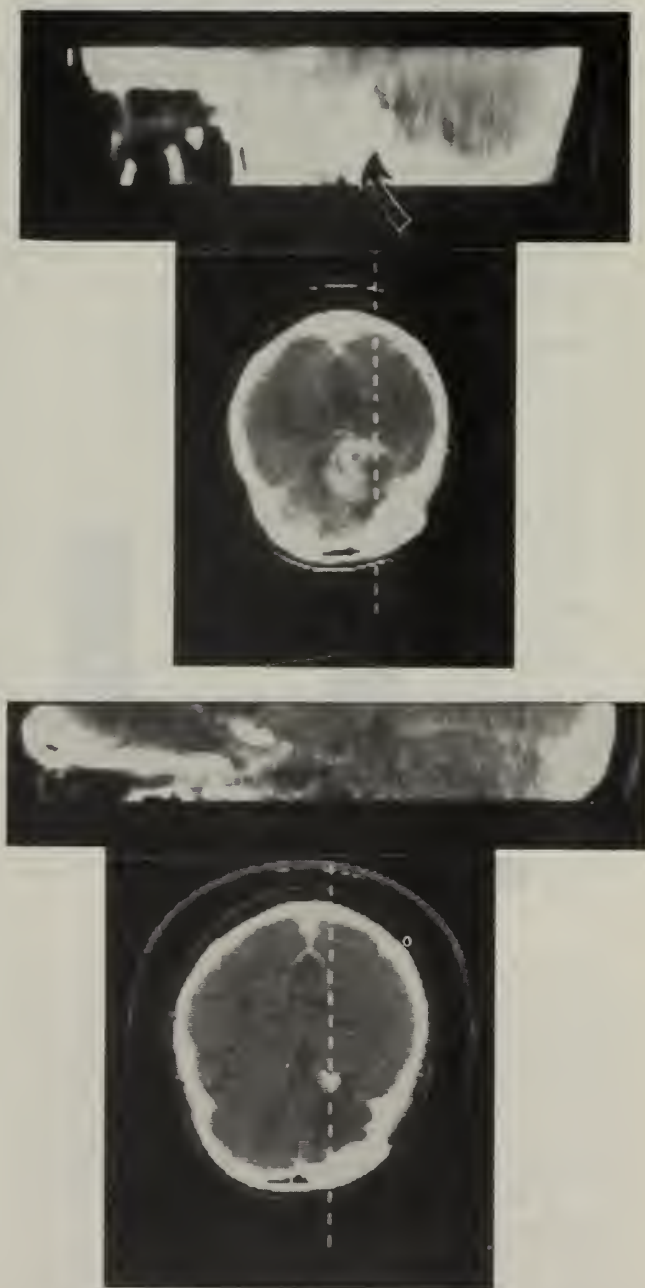
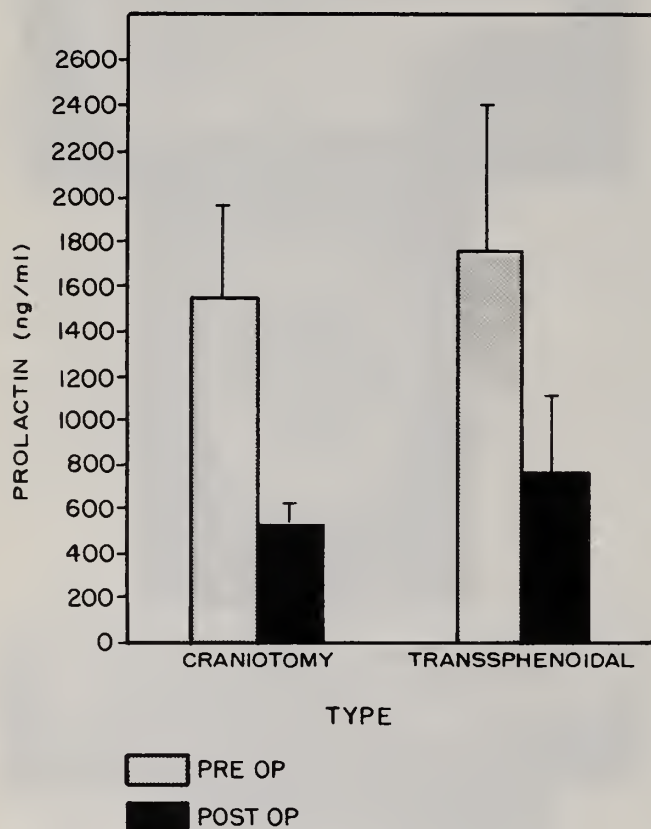


Figure 2. Computerized tomograms on RB, a 59 year-old female with macroprolactinoma occupying the whole sella and parasellar region (arrow, upper panel), prior to therapy, 5/17/82. On the bottom, 10/31/83, the large tumor has shrunk to a core of calcified tissue, post bromocriptine therapy.

Figure 3 shown the results of 16 patients who underwent surgery. Thirteen of them had a macroprolactinoma and 3 a microprolactinoma. Preoperatively, the total mean prolactin level was over 1,500 ng/ml. Though postoperatively, total mean prolactin levels decreased, they still remained significantly elevated with mean value around 500 ng/ml. All these patients, except one, required bromocriptine therapy postoperatively in order to decrease prolactin levels to normal.

FIGURE 3. PROLACTIN LEVELS PRE AND POST SURGERY



The total outcome of the 16 patients surgically treated is shown in Table 5. Only one patient was cured. This one had a microadenoma. On the other hand, 7 of 16 (44%) had some complication postoperatively. Surgery failed to correct the marked visual defects initially present in 10 patients. Indeed, 2 developed permanent blindness postoperatively. Other complications included secondary adrenal insufficiency in 2 patients, diabetes insipidus in one, another had CSF leak, and one developed hypopituitarism.

Among 28 patients who used bromocriptine as prescribed, a complete response was obtained in 20 (70%) and a partial response in 8 (30%) as shown in Table 6.

In only 5, bromocriptine was discontinued because of poor tolerance to the medication. Three patients reported nausea and abdominal discomfort, one felt drowsy and another showed tiredness and constipation.

Table 5

Outcome of Surgically Treated Hyperprolactinemic Patients		
	Number of Patients	(%)
Cured	1	(6.2)
Complications (n=7)		
Progression to permanent blindness	2	(12.5)
Adrenal insufficiency	2	(12.5)
Diabetes insipidus	1	(6.2)
CSF leak	1	(6.2)
Hypopituitarism	1	(6.2)

Table 6

Outcome of Treatment with Bromocriptine Among Compliant Patients		
	Number of patients	(%)
Complete response	20	(71)
Partial response	8	(29)
Total	28	(100)

Discussion

In recent years an increasing number of physicians have been prescribing bromocriptine mesylate as initial therapy for micro and macroprolactinomas. Prior to the availability of this dopamine agonist, treatment for such tumors was mainly surgical. However, the incidence of postoperative recurrence of prolactinomas remains high.

One study reported a 50% rate of recurrence within 4 years after surgery in 24 women with microadenomas and 80% recurrence rate within 2-3 years in 5 women with macroadenomas.¹ Also, surgery entails the risk of losing all pituitary functions and the subsequent need for multiple replacement therapy.²

Our experience reveals that 15 of 16 patients surgically treated required bromocriptine therapy postoperatively irrespective of the type of neurosurgical approach used, i.e. transsphenoidal vs. craniotomy, with an overall recurrence rate of 94%. Of these patients, 13 had a macroadenoma and 3 a microadenoma. Only one patient who had a microadenoma was identified as being "cured".

Recurrence rate was 100% for macroadenomas and over 60% for microadenomas. On the other hand, 7 of 16 operated patients had postoperative complications. Selective or complete pituitary insufficiency was manifested in 4 patients and 2 developed permanent blindness. None of the patients with visual field defects had improvement postoperatively.

The introduction of bromocriptine treatment for prolactinomas met initially with some resistance or reluctance by most neurosurgeons especially in the presence of visual field impairment, usually associated with a macroadenoma.

They argued that tumor size reduction was just a reflection of hormonal cell degranulation. However, Gen et

al¹² showed unmistakable evidence of tumor necrosis and fibrosis among 6 patients with big tumors, treated with bromocriptine and subsequently submitted to operation.

This prompted a Multicenter Bromocriptine Trial (eleven institutions in Europe & America), the results of which were summarized by Molitch et al in 1985.³ They analyzed 27 patients with macroprolactinomas treated only with bromocriptine. Reduction in tumor size was observed by CT in all patients. In 19 patients, reduction in tumor size was evident after 6 weeks of therapy. In eight patients decrease in tumor size was noted after six months of therapy. Improvement of visual field defects were observed in 9 of 10 patients who initially had visual field abnormalities. These investigators recommended that therapy with bromocriptine should be considered as initial management for patients with prolactin-secreting macroadenomas.

There are at least 12 additional studies that have provided data on dramatic reductions in tumor size with improvement of visual field, relief of ophthalmologic findings and restoration of gonadal function.⁴⁻¹²

Of these, the most definitive study was that by Gen and collaborators¹² who, as previously mentioned, showed histopathologically that bromocriptine therapy could have a direct cytolytic effect on lactotrophs of prolactinomas as an important cause for reduction in tumor size, restoration of visual field defects, and decrease in prolactin levels.

In three of our patients with macroadenomas, who had bromocriptine as primary therapy, there was a significant reduction in tumor size in all. No visual field defects were detected in these patients. In view of our experience, we advocate the use of bromocriptine as primary therapy even in those with visual impairment as surgery does not appear to guarantee improved vision.

It is thus apparent that surgery would only be considered as an option reserved for patients with macroprolactinomas who experience a continuous growth of tumor with persistent hyperprolactinemia and worsening of visual field defects in spite of adequate bromocriptine therapy, and/or significant intolerance to medication in spite of remedial actions, i.e. careful, gradual increase of initially small doses ($1/4$ to $1/2$ tab of 2.5 mg) with meals, and beginning at bedtime.

It is important to be completely sure that we are dealing with a true macroprolactinoma and not with a large non-functioning pituitary adenoma or a suprasellar mass that can cause hyperprolactinemia due to stalk or hypothalamic compression. In the latter situations serum prolactin levels are usually under 200 ng/ml. Under such circumstances, bromocriptine therapy will not cause reduction in tumor size nor improvement of visual field defects and may obscure the efficacy of bromocriptine in true macroprolactinomas.

There is an isolated report that suggests benefit in the management of some patients with "functionless" pituitary tumors in whom surgery or radiotherapy is not considered but that treatment may have to be continued for one year or more before benefit is recognized.¹³ This remains unconfirmed by others.

Some authors have suggested that initial bromocriptine therapy, reducing the size of prolactinomas, can make a

subsequent surgical removal safer.² However, other investigators argue that bromocriptine should not be used in patients with microprolactinomas, as their data pointed to lesser restoration of normal postoperative prolactin values in patients treated previously with the drug as compared to those who had not been treated preoperatively.¹⁴ This effect may be related to the observation that long term use of bromocriptine can lead to intraadenomatous fibrosis altering the consistency of an initially soft tumor tissue, making complete extirpation more difficult.¹⁵ On the contrary, in this study there was no difference in the macroadenoma group which historically is more prone to a surgical approach.

It is indeed known that most if not all patients with macroprolactinomas revert to previous elevations of prolactin and tumor reexpansion, upon discontinuation of bromocriptine although the latter expansion could turn out to be a secondary empty sella.

It is unresolved whether tumor shrinkage could be better studied and followed-up by more discerning techniques such as gadolinium-magnetic resonance imaging.

The present study supports the view that bromocriptine should be the initial treatment of choice to treat hyperprolactinemic patients, that only in unusual instances would a neurosurgical approach be justified, and that patients must be alerted about the likely need for continued postoperative treatment with a dopamine agonist drug.

It must be stressed that a major advantage of bromocriptine therapy over surgery is that a significant reduction in tumor size avoids the risk of subsequent hypopituitarism.

In summary, bromocriptine proved to be a uniformly good treatment and a well tolerated drug among our hyperprolactinemic patients, while a neurosurgical approach had a very low cure rate and a relatively high incidence of postoperative complications. It must be stressed that significant visual impairment should not longer be regarded as an obligatory indication for neurosurgical therapy in patients with macroprolactinomas.

Bromocriptine appears nowadays to be the initial treatment of choice for both micro and macroprolactinomas.

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FE DE ERRATA

Por error de impresión no aparecen los nombres de Alberto E. Sánchez, MD y Myrtha L. Santana, RN como los autores del artículo titulado: "Mamoplastía de Reducción: ¿Salud o Belleza? Este artículo aparece en la página 163 del Boletín de la Asociación Médica de Puerto Rico correspondiente al mes de mayo de 1989.

La Junta Editora le pide excusas a los autores por los inconvenientes que dicho error pueda ocasionarles.

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Dr. Holwick in operating room at Letterman Army Medical Center.

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Enfermedad Inflamatoria del Tracto Gastrointestinal en el Hospital Universitario, Centro Médico, Puerto Rico. 1980-87

José M. Moreno, MD
Carlos E. Rubio, MD, FACP
Esther A. Torres, MD, FACP

Resumen: A pesar de ser conocidas la colitis ulcerativa y la enfermedad de Crohn hace mucho tiempo, continúa sin establecerse su etiología, y se dificulta muchas veces distinguir una de la otra. Además sus características dificultan el estudio epidemiológico de la enfermedad.

En este trabajo se revisaron 70 expedientes con diagnóstico definitivo de enfermedad de Crohn y colitis ulcerativa y se compararon los resultados con la literatura de otras partes del mundo. Encontramos que la proporción de colitis ulcerativa a enfermedad de Crohn es alta, 5.4:1, no hubo variación con respecto a los grupos etáreos afectados ni a los síntomas más frecuentes; pero sí hubo variación en los patrones de enfermedad de Crohn, siendo el colónico el más frecuente. También se encontró un porcentaje bajo de manifestaciones extraintestinales. Esto hace pensar en la necesidad de seguir un protocolo adecuado para la evaluación de pacientes con enfermedad inflamatoria del intestino.

La enfermedad inflamatoria del tracto gastrointestinal (conocida en inglés como "Inflammatory Bowel Disease"), comprende dos entidades: la colitis ulcerativa y la enfermedad de Crohn.

La colitis ulcerativa fue descrita en 1875 por Wilks y Moxon¹ y la enfermedad de Crohn fue reconocida en 1932 por Crohn, Oppenheimer y Ginzburg.² En esa época se pensaba que involucraba solo intestino delgado y se conocía como ileitis regional; en 1960 Lockart y Morson demostraron la presencia de enfermedad de Crohn afectando también el colon total o parcialmente, con o sin enfermedad del intestino delgado concomitante.^{2, 3}

Ambas condiciones presentan un reto diagnóstico, especialmente en áreas donde son menos frecuentes como en el trópico.^{4, 5, 6} La mayoría de la literatura disponible y muchos de los amplios estudios sobre enfermedad inflamatoria del intestino son del área de Escandinavia, Gran Bretaña, Israel y Estados Unidos.^{4, 7, 8, 9, 10, 11} Estos recalcan que debido a que la enfermedad inflamatoria del intestino es a menudo episódica y sujeta a remisiones espontáneas, el diagnóstico inicial puede ser encubierto por la terapia, cualquiera que sea, retrasándose el diag-

nóstico definitivo. Además, muchos pacientes con proctitis tienen manifestaciones leves y nunca asisten a un consultorio médico.

En nuestro país es aún más difícil el diagnóstico porque fácilmente pueden confundirse con colitis por bacterias invasoras o por parásitos, lo que obliga a hacer frotis o cultivos para *Entamoeba coli*, *Salmonella*, *Shigella*, y otros.

El propósito de este trabajo es presentar los pacientes con enfermedad inflamatoria gastrointestinal evaluados en el Hospital Universitario del Centro Médico de Puerto Rico desde enero de 1980 a junio de 1987.

Material y Métodos

Con autorización de la Sección de Investigación de la Administración de Servicios Médicos, se obtuvieron los expedientes de pacientes que habían sido dados de alta con el diagnóstico de enfermedad inflamatoria del intestino, colitis ulcerativa, enfermedad de Crohn o ileitis regional según la clasificación 55.9 y 536 del "International Classification of Diseases; 9th Review Clinical Modification" (ICD-9CM) y de pacientes con estos diagnósticos por procedimientos endoscópicos en la Sección de Gastroenterología, que no habían sido hospitalizados.

El criterio diagnóstico que se usó estuvo basado en los parámetros propuestos por Mendeloff¹² y Binder,⁸ excluyendo enfermedad infecciosa y separando completamente la endoscopia de la radiología.

Para colitis ulcerativa, al menos tres de los siguientes cinco criterios debían estar presentes: a) historial típico con diarreas o sangre y secreción mucopurulenta o ambos en las excretas por más de una semana o en episodios repetidos; b) hallazgos endoscópicos típicos con mucosa friable, granular, con ulceraciones, o ambas; c) histología con inflamación, d) hallazgos radiológicos de ulceraciones o compatibles con colitis ulcerativa; e) exclusión de hallazgos similares por anatomía patológica.

Para enfermedad de Crohn, al menos tres de los siguientes cinco criterios eran necesarios: a) historia de diarrea por más de tres meses; b) hallazgos típicos por endoscopia, con estenosis y/o segmentación; c) hallazgos radiológicos compatibles; d) hallazgos histológicos compatibles; e) aparición de fístulas, abscesos, o ambos en relación con la lesión intestinal.

Resultados

De los expedientes proporcionados se excluyeron 9 porque tenían otros diagnósticos. De los 104 restantes, 29 no aparecieron en el momento de la revisión por estar inactivos al no visitar por más de 3 años el hospital.

Se revisaron 75 expedientes, de los cuales 5 no llenaron los criterios diagnósticos. De los 70 restantes, 11 correspondieron a enfermedad de Crohn (16.71%) y 59 a colitis ulcerativa (84.28%), dando una proporción de colitis ulcerativa a enfermedad de Crohn de 5.36:1.

Distribución por Edad y Sexo

La distribución por sexo en enfermedad de Crohn fue: 6 hombres y 5 mujeres (1.2:1), y en colitis ulcerativa 27 eran hombres y 32 mujeres (.84:1).

Respecto a la edad cuando se hizo el diagnóstico en enfermedad de Crohn el mayor número (4 pacientes, 36.3%) fue en el grupo de 0-20 años y en colitis ulcerativa el mayor número fue 16 pacientes en cada grupo de 21-30 (27.1%) y de 31-40 años (27.1%), (Tabla I).

Tabla I - Edad y Sexo al Momento del Diagnóstico

Enfermedad de Crohn						
Edad	Hombres	(%)	Mujeres	(%)	Total	(%)
0-20	3	(27.3)	1	(9.1)	4	(36.4)
21-30	0	(0)	1	(9.1)	4	(9.1)
31-40	1	(9.1)	2	(18.2)	3	(27.3)
41-50	0	(0)	0	(0)	0	(0)
51-60	2	(18.12)	1	(9.1)	3	(27.3)
-60	0	(0)	0	(0)	0	(0)
Total	6	(54.6)	5	(45.5)	11	(100.1)

Colitis Ulcerativa

Edad	Hombres	(%)	Mujeres	(%)	Total	(%)
0-20	4	(6.78)	3	(5.08)	7	(11.86)
21.30	7	(11.86)	9	(15.25)	16	(27.11)
31.40	6	(10.17)	10	(16.95)	16	(27.12)
41.50	4	(6.78)	4	(6.78)	8	(13.56)
51.60	2	(3.89)	3	(5.08)	5	(8.47)
-60	4	(6.78)	3	(5.08)	7	(11.86)
Total	27	(45.76)	32	(54.21)	59	(99.98)

Tabla II - Duración de los Síntomas antes del Diagnóstico

	Número de Pacientes	
	Enfermedad de Crohn	Colitis Ulcerativa
<1 semana	0	2
1-4 semanas	1	2
>4 semanas- <3 meses	0	11
3 meses- <1 año	2	15
≥1 año	5	11
No establecido	3	17
Total	11	59

Complicaciones

Un paciente con enfermedad de Crohn que tenía cáncer en la flexura esplénica, desarrolló megacolon tóxico y fue sometido a cirugía, luego desarrolló sepsis, insuficiencia renal y falleció. Tres pacientes requirieron transfusión en algún momento por anemia severa (27.2%)

En colitis ulcerativa, once pacientes (18.6%) requirieron transfusión en algún momento, 4 (6.7%) cursaron con depresión severa que ameritó consulta siquiátrica; 3 (5.1%) tuvieron megacolon tóxico; 2 (3.3%) tuvieron obstrucción intestinal post cirugía; 1 (1.69%) desarrolló arritmia cardíaca durante una colonoscopia; 1 (1.69%) presentó hipersensibilidad a la azulfidina; 1 (1.69%) tuvo bacteremia; 1 (1.69%) desarrolló candidiasis oral mientras tomaba prednisona; 1 (1.69%) sufrió amputación de miembro inferior izquierdo debido a osteomielitis secundaria a extravasación de Intropia y necrosis durante manejo de un episodio de megacolon tóxico.

Estado de los Pacientes al Final del Estudio

De 11 pacientes con enfermedad de Crohn, 1 (9%) había fallecido; 7 (63.6%) estaban asintomáticos (3 con tratamiento y 4 sin él), y dos estaban sintomáticos con tratamiento (18%).

De cincuenta y nueve pacientes con colitis ulcerativa, 3 (5%) no asistieron a seguimiento después del diagnóstico; 4 (6.7%) tenían proctocolectomía y seguían asintomáticos.

Síntomas

Tanto en enfermedad de Crohn como en colitis ulcerativa los síntomas más frecuentes fueron: diarrea, dolor abdominal y hematoquezia, pero en diferentes porcentajes. (Tabla III). Se excluyeron 3 pacientes de colitis ulcerativa y uno de enfermedad de Crohn por no tener datos en expedientes.

Tabla III - Síntomas

Enfermedad de Crohn		%	Colitis Ulcerativa		%
diarrea	8	80%	diarrea	48	85.71
dolor abdominal	8	80	hematoquezia	44	78.57
hematoquezia	7	70	dolor abdominal	34	60.71
fistula/fisura	5	50	pérdida de peso	24	42.86
mucosidad	5	50	mucosidad	17	30.36
pérdida de peso	4	40	tenesmus	12	21.43
nausea o anorexia	3	30	nausea o anorexia	6	10.71
tenesmus	2	20	fistula/fisura	1	1.79

Extensión de la Enfermedad

Un paciente de enfermedad de Crohn tenía una colectomía y fue excluido del análisis. Los restantes diez tenían sigmoidoscopia y/o colonoscopia; solo 5 se les había hecho enema baritada y a 6 se les hizo radiografía del intestino delgado, con estos estudios se identificaron los siguientes patrones: ileocólico en 1 paciente (10%) y colónico en 9 (90%). Ningún paciente tenía enfermedad limitada al intestino delgado o anorectal solamente.

De estos, por endoscopia superior se identificó lesión en esófago en el paciente con patrón ileocólico. Un paciente con lesión perianal se asoció a patrón ileocólico y 3 con lesión perianal se asociaron a patrón colónico.

Cincuenta y seis pacientes de colitis ulcerativa tenían estudios endoscópicos positivos, de éstos solo 34 tenían estudios radiológicos (enema baritada: 29, radiología de intestino delgado: 5). (Tabla IV)

Tabla IV - Patrón de Enfermedad en Colitis Ulcerativa: Endoscopia vs Radiología

Patrón	Endoscopia		Enema Baritada		%
	# (56)	%	# (29)	Positivo	
Proctitis					
Proctosigmoiditis	31	55.35	16	7	43.7
Colitis lado izquierdo	16	28.57	7	100	
Colitis universal	8	14.28	5	3	60
Inactividad y cáncer	1	1.28	1	1	100

* (Este porcentaje se refiere a la efectividad del estudio comparado con la extensión confirmada por endoscopia).

Solo un paciente (1.78%) tenía ileitis de reflujo ("backwash ileitis") diagnosticado por radiología en un paciente con colitis universal.

Manifestaciones Extraintestinales

Dos de 11 pacientes con enfermedad de Crohn (18%) dieron historia de artritis y uno (9%) se presentó con placas y pústulas en piel.

De cincuenta y seis pacientes con colitis ulcerativa 3 (5.3%) tuvieron pioderma gangrenoso; 3 (5.3%) dieron datos de artritis o artralgias, en 2 (3.5%) se constató sacroilitis por radiografía y uno (1.7%) se presentó con eritema nodoso, para un total de 9 manifestaciones extraintestinales (16%).

Estudios Histológicos

En enfermedad de Crohn, 8 pacientes (72%) tenían estudio histológicos; todos estos tenían inflamación, en tres se encontró granuloma; en uno, cáncer y en ninguno se reportó displasia.

En colitis ulcerativa, 37 pacientes tenían estudios histológicos (66%), en 36 se encontró inflamación; en uno displasia y en uno cáncer.

Estudios de Laboratorio con el Diagnóstico

En enfermedad de Crohn, 8 pacientes (72%: 5 hombres y 3 mujeres) se presentaron con anemia (definida como menos de 12 gr Hb para mujer y menos de 14 gr Hb para hombres), dos estaban normales y en uno no aparecía resultado. Los cultivos de excreta se encontraron en solo tres pacientes (27.2%) y estos fueron negativos para bacterias patógenas. Análisis para huevos y parásitos en excretas se reportaron en 7 (63%) y todos fueron negativos.

En colitis ulcerativa 28 pacientes (50%) se presentaron con anemia: 13 mujeres (23.3%) y 15 hombres, (26.7%); 24 estaban normales y 4 no tenían datos. Del grupo de anemia 19 pacientes (67.8%) pertenecían al grupo de

colitis izquierda o universal. El cultivo de excretas se reportó en 22 casos, en uno se aisló *Klebsiella* y los restantes 21 fueron negativos para bacterias patógenas. Análisis para huevos y parásitos en excretas se informó en 34 pacientes de los cuales uno tenía *Trichuris trichiuris*, y 33 fueron negativos.

Tratamiento Médico

Un paciente con enfermedad de Crohn recibió azulfidina, 5 recibieron azulfidina y prednisona y metronidazole, y 2 no recibieron tratamiento.

De los pacientes con colitis ulcerativa, 24 recibieron azulfidina, 23 azulfidina y prednisona, 4 azulfidina, prednisona y cortisona, 4 azulfidina y cortisona y 1 prednisona solamente. Del grupo que solo recibió azulfidina, 13 (54.1%) tenían solo proctitis o proctosigmoiditis; los que recibieron azulfidina más cortisona, tenían proctitis o proctosigmoiditis.

Cirugía

Cuatro pacientes (36.3%) con enfermedad de Crohn al momento de la revisión habían sufrido las siguientes operaciones: 1 fistulectomía recto-vaginal, 1 hemicolectomía izquierda por fistulas refractarias, 1 colectomía por múltiples episodios, y 1 protocolectomía por cáncer (este paciente tuvo diagnóstico de colitis ulcerativa por 20 años, falleció por sepsis post-operatoria).

En el grupo de colitis ulcerativa, 8 (13.5%) de 59 pacientes han sido operados: 6 (2 hombres y 4 mujeres) se les hizo colectomía con anastomosis ileorectal por cáncer, y a otro se le hizo una colostomía por dilatación aguda (y luego cierre). Dos (3.38%) con protocolectomía no se les ha visto en 6 años; 1 (1.69%) con colectomía subtotal y anastomosis ileorectal está asintomático y con tratamiento; 35 (59.3%) estaban asintomáticos; 14 (23.7%) estaban sintomáticos (13 con tratamiento y 1 sin él).

Discusión

La incidencia y prevalencia de la enfermedad en el mundo es variable y aun no ha sido bien documentada, sin embargo en las pasadas dos décadas se han obtenido datos muy importantes que dan un rango combinado de incidencia de al menos 6-22 por cien mil en la población de raza blanca.^{4, 13}

En nuestro estudio no se proporcionan datos de incidencia y prevalencia porque solo se tomó como muestra un hospital y no representa a toda la población de Puerto Rico, además de que casi nunca especifica la raza debido a la variedad y mezcla de los grupos étnicos en la isla.

Otro inconveniente fue que no se pudo revisar un número significativo de expedientes,²⁹ limitado así el análisis de la muestra.

La proporción de colitis ulcerativa a enfermedad de Crohn en diferentes centros es variable, por lo difícil a veces de establecer las diferencias; pero estudios recientes dan una proporción de colitis ulcerativa de 2-3:1 en relación a enfermedad de Crohn,^{7, 14} que contrasta con la proporción de 5.36:1 encontrada en este trabajo. Esto puede deberse a la falta de reconocimiento de enfermedad de Crohn como se demostró tardíamente en un

paciente. La distribución por sexo fue similar a la que se ha encontrado en otros lugares.^{4, 17}

Generalmente la enfermedad de Crohn afecta al adulto joven de 15-30 años,^{10, 12, 14, 15} al igual que sucedió en nuestro grupo, pues combinando los grupos de 0-20 y 21-30 años se obtiene un 45%, mientras que para colitis ulcerativa se ha reportado que ocurre más de la tercera a la quinta década de la vida,^{10, 12, 14, 15} e igualmente sucedió con nuestros datos, pues los grupos de 21 a 30, 31 a 40 y 41 a 50 años comprendieron de 67.7%.

En cuanto a la presentación clínica en la enfermedad de Crohn, diarrea y dolor abdominal fueron los síntomas más frecuentes (80%), lo cual es prácticamente igual a lo reportado previamente.¹⁵

Aunque los síntomas en colitis ulcerativa varían de acuerdo a la extensión y/o severidad de la enfermedad, el sangrado es el síntoma predominante hasta en el 90% de los pacientes y puede acompañarse de diarrea, pérdida de peso y otros.^{5, 16, 17} En nuestra serie encontramos hematoquezia en el 78.5%.

La revisión más extensa de los patrones clínicos de enfermedad de Crohn¹⁸ establece el patrón ileocólico como el más frecuente (41%), luego sólo el intestino delgado (28.6%), colon (27%) y anorectal (34%), que contrastan con nuestros patrones, pues colon fue 90%, ileocólico 10%. Esto puede ser debido a una falla en buscar lesiones en intestino delgado por una clasificación errónea del paciente en el grupo de colitis ulcerativa.

Respecto a colitis ulcerativa, al igual que otros reportes¹⁷ la colitis más distal es la más frecuente y la de mejor pronóstico, y se confirma que para delimitar la extensión de la enfermedad el estudio endoscópico definitivamente es superior a la radiografía.^{19, 20}

Comparando los porcentajes de manifestaciones gastrointestinales con la serie más extensa²¹ solo pioderma gangrenoso en colitis ulcerativa, (5.3%) se acerca al 5% de esa serie, al igual que sacroileitis por radiografía (3.5%) pero esto depende de si se hace el estudio radiológico buscando esta patología. Artritis y eritema nodoso fueron raros y no hay ningún dato de otras manifestaciones, ya sea del grupo relacionado a colitis, relacionado a fisiopatología del intestino delgado, o no específicos. Esto sugiere que debemos ser más acuciosos buscando complicaciones en pacientes con enfermedad inflamatoria del intestino.

Llama la atención el alto porcentaje de anemia (72% y 50%) con que se presentaron los pacientes con enfermedad de Crohn y colitis ulcerativa respectivamente, y que está relacionado con la extensión de la enfermedad.

Con la clínica y evolución de otras patologías, se pudo establecer adecuadamente el diagnóstico en la mayoría de los pacientes, aunque idealmente todos deberían tener cultivo y examen de huevos y parásitos en excretas.

Se ha establecido que, respecto a manejo médico de la enfermedad inflamatoria del intestino, la azulfidina es muy efectiva en colitis ulcerativa leve y en prevenir recurrencias al igual que esteroides en etapas agudas. En la enfermedad de Crohn ambos pueden usarse en terapia inicial, pero ninguno garantiza profilaxis²² y se ha usado metronidazole en la enfermedad perianal.²³

El manejo que se ha dado en nuestros casos depende de las diferentes remisiones y exacerbaciones de la enferme-

dad, del cumplimiento de los pacientes, y de la apreciación del médico.

Respecto a cirugía, el mayor estudio de enfermedad de Crohn²⁴ reporta altos porcentajes de cirugía, 58 al 91.5%, según el patrón intestinal pero durante un período de seguimiento mínimo de 7 años (promedio de 13 años). En nuestros pacientes se ha llevado a cirugía al 36.3%, este dato puede variar si se hace un seguimiento prolongado. Igualmente sucede con la colitis ulcerativa, y aquí con mayor importancia dada la frecuencia aumentada de cáncer a medida que pasa el tiempo,¹³ por lo que es indispensable un adecuado seguimiento endoscópico.^{20, 25} A largo plazo se ha reportado megacolon tóxico en el 8% de pacientes con enfermedad de Crohn como complicación que lleva a cirugía;²⁴ nosotros tuvimos 1 (9%) en éste período. En cuanto a colitis ulcerativa se observó megacolon tóxico en 5% mientras que otras series reportan del 1-2.5%.¹⁶

Referente al seguimiento a largo plazo en la enfermedad de Crohn se reporta una mortalidad del 6% directamente relacionada a la enfermedad y hasta un 12% por otras causas. Nosotros hemos encontrado una defunción (9%) por sepsis e insuficiencia renal operatoria curiosamente en un paciente que por 20 años se catalogó como colitis ulcerativa.

El 63% estaba asintomático en su última consulta. En cuanto a colitis ulcerativa no ha habido, al menos reportada, ninguna defunción durante el período evaluado y el 67.7% está asintomático ya sea con manejo médico y/o quirúrgico, que refleja un adecuado cumplimiento y seguimiento de los pacientes.

Debido a lo complejo que resulta obtener datos adecuados de los expedientes, y la dificultad frecuente de diferenciar la enfermedad de Crohn de la colitis ulcerativa y con la ventaja de poder hacer posteriormente un estudio prospectivo, recomendamos aplicar el protocolo para enfermedad inflamatoria del intestino de la Organización Mundial de Gastroenterología⁹ o usar el sistema de puntos simplificado propuesto por la misma organización especialmente para distinguir la enfermedad de Crohn de la colitis ulcerativa.

Abstract: Although ulcerative colitis and Crohn's disease have been known for a long time, the etiology is still unknown, and at times it is difficult to distinguish one from the other. In addition, the characteristics of the disease make their epidemiologic study difficult.

We have reviewed 70 cases with the diagnosis of Crohn's disease or ulcerative colitis, and compared our results with those published from other parts of the world. We found a high proportion of ulcerative colitis to Crohn's disease, 5.36:1. There was no difference in affected age groups or most frequent symptoms; but we found Crohn's disease to be more frequent in the colon. We also found a very low incidence of extraintestinal manifestations.

We believe an adequate standard protocol should be followed for the evaluation of patients with inflammatory bowel disease, including complementary studies to assess disease patterns and complications.

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Case Presentation

Toxoplasmosis Simulating Progressive Multifocal Leukoencephalopathy

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Toxoplasmosis of the central nervous system has been increasingly associated with HIV infections. It usually presents in computed tomography as an enhancing mass lesion. In the case described by Blum et al on progressive multifocal leukoencephalopathy (PML) in AIDS,¹ they point out that the radiological differential diagnosis of PML includes granulomatous disease; astrocytoma and primary CNS lymphoma. We recently evaluated a case of cerebral toxoplasmosis presenting with the typical CT findings of PML.

Case Report

A 29 year old man parenteral drug abuser was found unconscious without evidence of head trauma. On admission, he was disoriented and restless, with no fever or nuchal rigidity.

His neurological examination revealed a mild right hemiparesis. CT scan demonstrated multiple low density

areas confined to white matter with scalloped lateral borders apparently respecting the cortical junction and without a mass effect or contrast enhancement (Fig. 1). A spinal tap showed: opening pressure 130 mm H₂O, white cells 1/mm³, glucose 59 mg% (serum 99 mg%), and protein 87 mg%. India Ink smear and VDRL were negative. A presumptive diagnosis of AIDS and PML was made. Septicemia by *Salmonella* was identified. The patient continued to deteriorate and died after ten days of hospitalization.

At autopsy, several areas of white matter necrosis, corresponding to the CT lesions, were evident. On microscopy, many *Toxoplasma gondii* cysts were found in the previously mentioned areas without the histological changes of PML. Search for papova virus particles by electron microscopy proved unsuccessful.

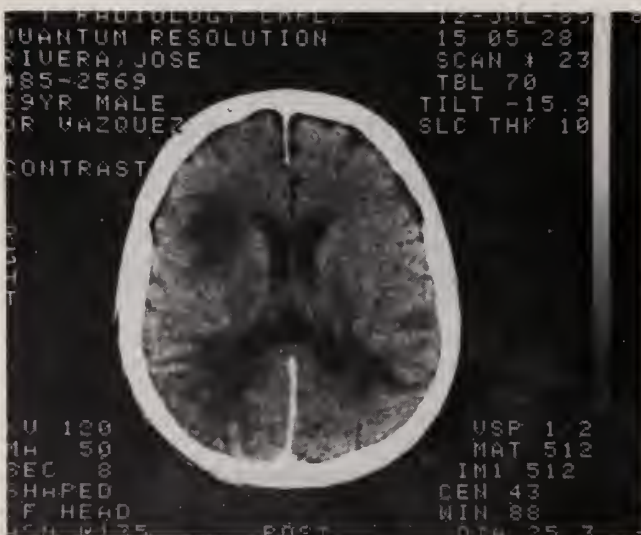
Discussion

Cerebral toxoplasmosis is common in the immunocompromised host.²⁻⁵ Toxoplasmosis has become the most common parasitic central nervous infection in AIDS in Puerto Rico. Of the first 100 AIDS autopsies seen by the Department of Pathology of the University of Puerto Rico School of Medicine, 21% had *T. gondii* confirmed in brain (Climent et al unpublished).⁶

The typical CT findings of cerebral toxoplasmosis consist of multiple enhancing nodules or rings usually associated with mass effect, with a predilection for basal ganglia, thalamus, corticomedullary junction, cerebellum, and white matter.⁷ Subcortical non-enhancing hypodense lesions have rarely been described in the literature.³⁻⁷

The CT in PML characteristically shows low density unenhancing white matter lesions with irregular lateral borders that follow the contours of the subcortical gray-white junction. In most cases, no mass effect is present.^{8,9} The radiological pattern in our case is indistinguishable from that of PML.

To our knowledge, the radiological presentation of cerebral toxoplasmosis in this case has not been previously reported.



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Ebstein's Anomaly in a Patient with Down's Syndrome

Charles D. Johnson, MD, FACC
 Pedro M. Ortiz-Colom, MD
 Héctor Sainz de la Peña, MD
 Elvira Barroso, MD

Summary: This communication describes a patient with Down's syndrome, in whom an Ebstein's anomaly of the tricuspid valve was found at autopsy. The association of these two conditions appears to be rare.

Down's syndrome or "Mongolism" occurs in approximately 1.45 per 1000 live births.¹ The predominant trisomy-21 form of the syndrome is the most common human chromosomal aberration and occurs in approximately 1 of every 600 neonates. It was first described in 1866 by Langdon Down.² Congenital heart disease is found in 35-50% of patients with the Down syndrome.³⁻⁷ The most characteristic and common cardiac defect is an endocardial cushion or atrioventricular canal defect. But, a ventricular septal defect (VSD), a secundum atrial septal defect (ASD), a patent ductus arteriosus (PDA), tetralogy of Fallot and most congenital heart defects have been encountered. Transposition of the great arteries (TGA) and coarctation of the aorta occur infrequently.^{1, 3-7} Moreover, the presence of an Ebstein's anomaly has been rarely observed in Down's syndrome, the authors having uncovered only two or three such cases from reports and reviews of individual Down syndrome and Ebstein anomaly patients.^{6, 8-9}

We wish to describe a patient with Down's syndrome in whom an Ebstein's anomaly, itself a rare defect (prevalence of 0.5% among patients with patients with congenital heart disease),⁹ was found at autopsy.

Case Report

This 17-year-old female with clinical Down's syndrome was admitted to a private hospital with cyanosis and decompensated congestive heart failure. The patient's condition worsened, with respiratory failure requiring mechanical ventilation for a month. It was difficult to wean the patient from the ventilator; a tracheostomy was performed. The patient was transferred to the University Hospital for further management.

Physical examination revealed a "typical mongoloid" appearance, with obesity, abducted hips and a hypothyroid demeanor. There was no heart murmur, but cardiomegaly and congestive heart failure were present. The electrocardiogram revealed a normal sinus rhythm and

an electrical axis of approximately + 85°. The P waves were peaked in leads I, II, a VL and V₂. The ST-T waves were nonspecifically abnormal. An incomplete right bundle branch block pattern was present, with a S_I S_{II} S_{III} pattern, a small qrs complex in V₁ and a Rs in V₆. Chest x-rays showed increased pulmonary vascularity and bronchopneumonia. Anemia was present. Respiratory failure with an acute respiratory distress syndrome, chronic disseminated intravascular coagulation, seizures and atrial flutter all appeared. Multiple antibiotics were administered, and finally she was weaned from ventilation. Soon afterwards, fever, diarrhea (Klebsiella), cyanosis and severe hypoxemia, cardiorespiratory arrests, and death followed.

Autopsy Findings (Figures 1, 2)

The weight of the heart was 450 gm. (enlargement); the epicardium was smooth and glistening; the right atrium measured 0.2 cm. in thickness and the cavity was larger than usual; the right ventricle measured 0.8 cm. in thickness, and the cavity was smaller and the wall thicker than normal. The left atrium measured 0.2 cm. in thickness, and the left ventricle 1.5 cm. The pulmonic valve was 1.5 cm. and the aortic valve 1.5 cm. in diameter. The foramen ovale was closed. The interventricular and interatrial septae were intact; the left and right coronary arteries were patent. The myocardium was firm and raddish-



Figure 1. Lateral view of the right heart chambers. On the top the right atrium is seen, and on the bottom the right ventricle, with the hypoplastic tricuspid valve.



Figure 2. This view shows the right ventricle with the tricuspid valve displaced inferiorly. The pulmonic valve is seen in the upper portion of the photograph. Note the triangular shape of the right ventricle.

brown, and the endocardium was smooth and glistening. The tricuspid valve measured 3.4 cm. in diameter and showed redundant valve tissue with restricted mobility of the septal and posterior leaflets which were attached to the septal wall; the insertion was also altered being lower than average.

Discussion

Ebstein's anomaly of the heart, first described by Wilhelm Ebstein of Breslau, Germany in 1866,¹⁰⁻¹² comprises a downward displacement of a dysplastic tricuspid valve into the right ventricle (RV). The RV is small and the right atrium (RA) is correspondingly dilated. A patent foramen ovale or a secundum atrial septal defect is present in over one-half of the cases, and pulmonary stenosis or atresia are often observed. A small ventricular septal defect, a patent ductus arteriosus coarctation of the aorta, tetralogy of Fallot, and other defects are less frequently present. Patients with corrected transposition of the great vessels may have a "left-sided" Ebstein's malformation.¹³⁻¹⁶ Ebstein's anomaly has been associated also with Bonnevie-Ullrich, and with Marfan's syndromes.⁹

This patient also presented thyroid gland atrophy with hypothyroidism,^{17, 18} bilateral hip dysplasia,¹⁹ and respiratory failure,^{20, 21} all of which have been reported in the Down's syndrome.^{22, 23}

Resumen: Este comunicado describe a un paciente con síndrome de Down al cual se le encontró anomalía de Ebstein de la válvula tricuspídea en la autopsia. La asociación de estas dos condiciones parece ser rara.

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BRIEF COMMUNICATIONS

Prostatic Cancer with Metastasis to the Penis

Juan R. Iturregui-Pagán, MD, FACS, FAAP
Oscar Trujillo, MD

Secondary tumors of the penis are extremely rare. Only 200 cases approximately have been reported in the literature.¹ The primaries are mainly of genitourinary or gastrointestinal origin.² The 218 collected by Powell in 1985, were principally of the following origin: bladder (6), prostate (65), rectosigmoid (34) and kidney (23).³

We herein present a case of prostatic cancer with penile metastasis. Various aspects of this disease are discussed.

Case

A 72 years old patient was referred to our Center with a history of progressive prostatism and painless induration of the penis causing deviation on erection. The physical exam showed a lesion in the cavernous body, resembling a Peyronie's plaque and the prostate was hard. He was admitted at the Urology Service where a transurethral resection of the prostate was performed with biopsy of the penis lesion. The pathologic study in both specimens revealed the presence of a prostatic adenocarcinoma (Figs. 1-2) The patient is receiving hormone therapy without complications.

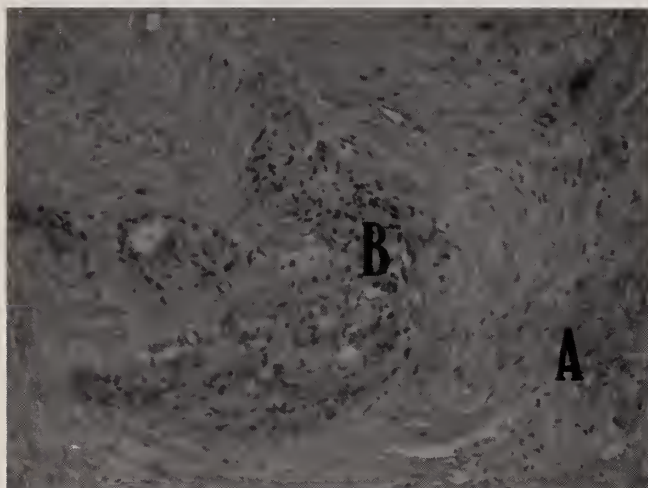


Figure 1. Microscopic section (4X) showing tunica albuginea of corpus cavernosum (A) invaded by malignant epithelium (B).



Figure 2. Same as figure 1 but 10X.

Discussion

Secondary tumors of the penis are rare, but usually of poor prognosis as it indicates disseminated disease. Usually, presents as priapism, due to the tumoral obstruction of the cavernous body. This was called malignant priapism by Peacock, though the first case was reported by Eberth on 1870.⁴ Other forms of presentation are nodules in the *tunica albuginea*, perineal pain or penis edema. Involvement of both cavernous bodies has been described. Invasion of glans or *corpus spongiosum* is rare. These lesions must be differentiated from the lesions of Peyronie's disease, scars due to trauma or infections, or thrombi.

In 1956 Paquin and Roland described the invasion mechanism, that is by direct extension, through venous or lymphatic channels or by arterial thrombi.⁵

The highest survival period reported in cases of prostatic tumors has been 7 years,⁶ but usually the prognosis is very poor and most patients die in the first year.

Therapeutical modalities include: local excision, penectomy, radiotherapy and chemotherapy.⁷ As it is a manifestation of disseminated disease, the treatment should be symptomatic.

The presentation of this case as a Peyronie's plaque reveals the importance of meticulous evaluation of all, even the benign looking, penile lesions.

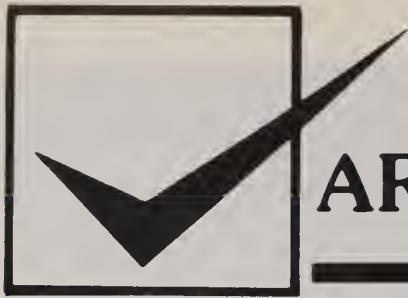
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Sirviendo al Pueblo y a la Profesión Médica



ASOCIACION MEDICA DE PUERTO RICO



ARTICULO ESPECIAL

Tendencias Futuras en los Servicios de Salud de Puerto Rico*

Juan R. Colón Pagán, MD, FACG

El pueblo de Puerto Rico está preocupado por los servicios de salud. Cada vez que se hacen encuestas encontramos el problema de los servicios de salud entre los primeros diez. Durante la campaña eleccionaria el "issue" de la salud estuvo en la "picota" pública y preguntamos, ¿por qué? Puerto Rico tiene una expectativa de vida de las más altas en el mundo. La tasa de mortalidad ha disminuido a una de las más bajas en el mundo y la mortalidad infantil continua disminuyendo. La queja es de todos los pacientes como de los proveedores incluyendo, los hospitales, los médicos, enfermeras y todas las profesiones aliadas en algún momento se quejan de los servicios de salud tanto públicos como privados.

Hace más de 100 años se estableció el primer servicio de salud privado tipo HMO (Organización Mantenimiento de Salud) administrado por el Hospital Auxilio Mutuo y que existe todavía. Nosotros nos adelantamos a este tipo de organización muy utilizado en las últimas décadas en los Estados Unidos. En el 1912 se creó el Departamento de Salud y los servicios gubernamentales de salud fueron centralizados a través de esta dependencia. Durante los últimos 60 años hemos visto un crecimiento del servicio privado utilizando las asociaciones independientes de seguros y los seguros por indemnización como intermediarios del pago por servicios a los proveedores. Actualmente, le ofrecen servicios a 50% de nuestra población y el estado se responsabiliza a proveer los servicios de salud de otro 50% de la población. Analicemos todo esto en su propia perspectiva.

Los pacientes requieren mejores servicios. Quieren que los servicios estén disponibles cuando los necesiten, que sean atendidos con prontitud y esmero, utilizando la tecnología más avanzada, y exigen que el profesional tenga el adiestramiento más completo, por el cual le hacen responsable. La incidencia de demandas por responsabilidad profesional, ("malpráctica"), ha ido aumentado en Puerto Rico en los últimos años.

No existen los fondos disponibles necesarios para dar los servicios que el pueblo quiere, necesita y exige. No existe el dinero necesario para dar los servicios que el proveedor quiere y debe ofrecer. Así es que tenemos que analizar cómo podemos resolver este problema.

El Departamento de Salud ha manejado los servicios de salud por los últimos 75 años, y está en una posición sumamente precaria. Tiene un presupuesto sobre \$500 millones, incluyendo los programas federales, tiene un déficit de \$200 millones, una expectativa de déficit de \$100 millones para este próximo año, y asociado con demandas multimillonarias sobre \$1,000 millones. El futuro es oscuro. El "paciente" está muy enfermo. Va a haber la necesidad de hacer cirugía mayor y/o de desarrollar unas mejores estrategias. Se comenzó para la década del 60 con el concepto de regionalización cuando llovieron los millones de dólares bajo la Ley Hill Burton. Creímos en esa forma de resolver el problema, pero tampoco la encontramos efectiva.

El sistema privado también le ha fallado al pueblo de Puerto Rico. Las instituciones hospitalarias no se han desarrollado según las expectativas de los proveedores y los consumidores. No se proveen los equipos necesarios para ofrecer unos servicios dentro de la institución y en estos momentos está en una situación precaria económicamente. Hay sobre 2,000 camas en Puerto Rico que no son necesarias y cuestan mucho dinero. Hemos llegado al fondo del barril.

No existen los recursos económicos, pero tampoco hay un sistema para generarlos. Hay unos sub sistemas que están desarticulados, contamos con un "reguerete" de instituciones hospitalarias, un "reguerete" de profesionales y no hemos tenido la debida planificación estratégica necesaria para llevarnos al año 2000.

La unidad de planificación del Departamento de Salud ha sido desmantelada en los últimos 20 años. ¿Cuál es el porvenir? La primera parte tiene que ser el establecimiento de una planificación estratégica y ya se están tomando las medidas para esto.

El sistema de financiamiento es importante y hay que analizarlo. Las únicas tres fuentes de financiamiento que tenemos son la Legislatura de Puerto Rico, el Gobierno Federal y los Seguros Médicos.

El alto costo de los seguros y los servicios continuarán

Presidente Consejo General de Salud, Departamento de Salud, Estado Libre Asociado de Puerto Rico.

**Presentado ante Health Finance Management Association Meeting, el 8 de marzo de 1989, Hotel Condado Plaza, San Juan, Puerto Rico.*

subiendo. No vamos a poder pararlos. El Sr. Toby nos acaba de informar que Medicare va a tener que controlar en cinco millones de dólares este próximo año. Los controles de costos son necesarios y hay dos formas: controlando la utilización y controlando el pago a los proveedores. Las dos son malas. Tenemos que continuar buscando formas de mantener los costos bajos en Puerto Rico. Aunque al compararlo con los E.E.U.U. los nuestros son bajos.

Los seguros médicos seguirán aumentando. Tendrán una reorganización y quedarán aquellos más eficientes administrativamente y que provean alternativas de seguros para toda la población, al costo más bajo. No podemos continuar con campañas publicitarias millonarias de relaciones públicas de estas instituciones en detrimento de los servicios que se ofrecen y el pago a los proveedores. Considero necesaria la intervención de la Legislatura, del Comisionado de Seguros y la acción concertada de los proveedores y consumidores para que exijan lo antes expresado.

No creo que habrá un seguro único del gobierno después de la experiencia de 1973 con la Comisión de Seguros de Salud Universal. El estudio de esta demostró que es imposible originarlo en Puerto Rico.

La responsabilidad económica del gobierno para los servicios de salud tendrá que transferirse hacia los patronos y de estos hacia los empleados. Los patronos tendrán que participar activamente como lo han hecho en los EE.UU. en financiar programas de seguros de salud para sus empleados.

La participación de proveedor del gobierno debe ir disminuyéndose. El Programa de Medicaid debe implementarse en Puerto Rico en la forma igual que se ha implementado en todos los estados de la Nación Americana. Es sumamente importante que se mantenga la libre selección de médicos, la libre selección de hospital y la libre selección de poder escoger un seguro médico. El financiamiento de los médico-indigentes continuará entre el gobierno estatal y el gobierno federal y se mantendrá a través de los impuestos.

El pago a los médicos lo veremos cambiar en el futuro a través de un sistema de pago relacionado a la especialidad (RBRVS). Tardará mucho en que los pagos por grupos por diagnóstico (DRG's) llegue a ser el pago de médicos. Posiblemente la Asociación Médica Americana combatirá esto hasta el máximo. Ya han sido aceptados los sistemas de pago por capitación en los médicos generalistas y médicos de familia. Más médicos estarán empleados y más uniones de médicos se crearán para el establecimiento de la negociación necesaria entre ambos.

Se crearán organizaciones sin fines pecuniarios para ofrecerle servicios a distintos grupos como los envejecientes, los médico-indigentes, y otros. Organizaciones sin fines pecuniarios que tendrán la credibilidad y el conocimiento administrativo para poder ofrecer servicios y utilizarán todos los mecanismos de financiamiento necesarios existentes para este tipo de organización.

Reevaluaremos los programas presentes como Auxilio Mutuo, Asociación de Maestros, etc. y buscaremos la forma de modificarlos para que lleguen a ser eficientes y efectivos. Los centros de salud podrán entrar en experimentos de privatización (la palabra privatización no la

quiero decir aquí en el concepto de las experiencias pasadas negativas sino en el concepto de *comunidades*). La comunidad tendrá participación activa en el manejo de ellos. Habrá unos servicios ofrecidos hacia el mantenimiento de salud, y a la prevención que es hacia donde los servicios de salud se moverán.

La accesibilidad a los servicios de salud tendrá que mejorarse, intensificando los servicios de emergencias médicas, crearse un número de teléfono exclusivo para emergencias y aspiro que algún día los servicios de emergencias médicas se unan al servicio de bomberos para integrarlos como un servicio paramilitar de servicios de salud igual que se ha visto en otras áreas de la Nación Americana.

Los servicios de envejecientes irán desarrollándose. Estos servicios son necesarios porque es una población que va creciendo constantemente y necesita servicios. No existe la infraestructura en Puerto Rico preparada para estos servicios y hay que proveerla. Se le dará más importancia a los servicios en el hogar, por estar cerca del núcleo familiar y donde el envejeciente deberá recibir gran cantidad de servicios.

El ciudadano deberá desarrollar responsabilidad por el cuidado de su salud. Esta responsabilidad operará para que no se mal utilicen los servicios. Será necesario establecer un sistema educativo en salud en las escuelas de Puerto Rico a todo lo largo y ancho del sistema. Una persona educada, que pasa por una escuela por sobre doce años definitivamente tiene los elementos de juicio para poder tener una mayor responsabilidad en el cuidado de su salud. Recuerden que el 66% de las causas de muerte en Puerto Rico están relacionadas con el estilo de vida. Si nosotros pudiésemos lograr que nuestros conciudadanos estableciesen un estilo de vida adecuado, podríamos disminuir muchísimos de los problemas de salud presentes.

La prevención y el cuidado de salud tiene que ser piedra angular de los servicios de salud en Puerto Rico. Las facilidades de salud tendrán que mirar hacia el hospital como la institución centro, la institución eje de la unidad de servicios. Es la institución quien tiene la organización administrativa para ofrecer servicios de salud completos. Veremos un hospital en el futuro completamente diversificado: en servicios de salud en el hogar, clínicas satélites y diversificación en otras áreas inclusive ofreciendo servicios de comidas en las casas para pacientes para una mejor utilización de sus cocinas.

Las experiencias en los E.E.U.U. han demostrado que sobrevivirán aquellas instituciones que tengan visión y desarrollen la planificación estratégica adecuada, que ofrezcan un taller de trabajo al profesional que le satisfaga tanto a él como al consumidor, que le satisfagan sus expectativas. Los centros ambulatorios continuarán desarrollándose unidos a hospitales, o independientes, pero existirá una intercomunicación y la computadora vendrá a ser y a tener una importancia tremenda en Puerto Rico lo mismo que en otras áreas del diario vivir.

Como dijo la Dra. Carolyn Davis veremos la computadora comunicándose desde la casa del paciente, la oficina del médico a la institución hospital y existirá una intercomunicación completa para ofrecer unos servicios eficientes y efectivos.

Las facilidades públicas espero estén administradas por organizaciones sin fines pecuniarios y se utilice más la unión hospital-centro de salud. Necesitamos que estas instituciones se desarrollen con conocimiento de responsabilidad, con respaldo económico necesario y una experiencia administrativa. Se necesitará la creación de equipos administrativos como consultores y asesores para ayudar a estas instituciones en su desarrollo.

Los recursos humanos tendrán una redistribución de responsabilidades donde aquellas profesiones aliadas como la enfermera y la nutricionista trabajarán más activamente en los servicios de salud para ayudar al médico a maximizar sus esfuerzos y a darel mejor servicio. La interacción entre otros profesionales continuará aumentándose cada día. Veremos como el educador en salud asume una posición más prominente dentro del equipo de la

salud para ayudar en el proceso educativo de los pacientes y de los ciudadanos.

En resumen todos vamos a tener que ser eficientes, más efectivos, planificar estratégicamente nuestros movimientos y orientarnos hacia el mantenimiento de la salud y hacia la maximización de los recursos utilizando la tecnología más avanzada. Debemos trabajar en equipo con metas y objetivos, control de presupuesto y los sistemas evaluativos adecuados. La remuneración de nuestros profesionales deberá ser adecuada en todas las profesiones, tanto aquellas que han sido rezagadas como las que están adelantadas y se deberá basar en la productividad, experiencia y adiestramiento. Tenemos que tener más visión y planificar adecuadamente, pero no olvidando nuestra misión que es servir. Servir, orientar y educar.

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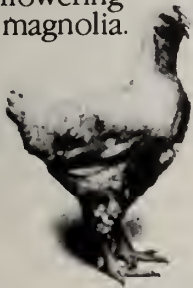
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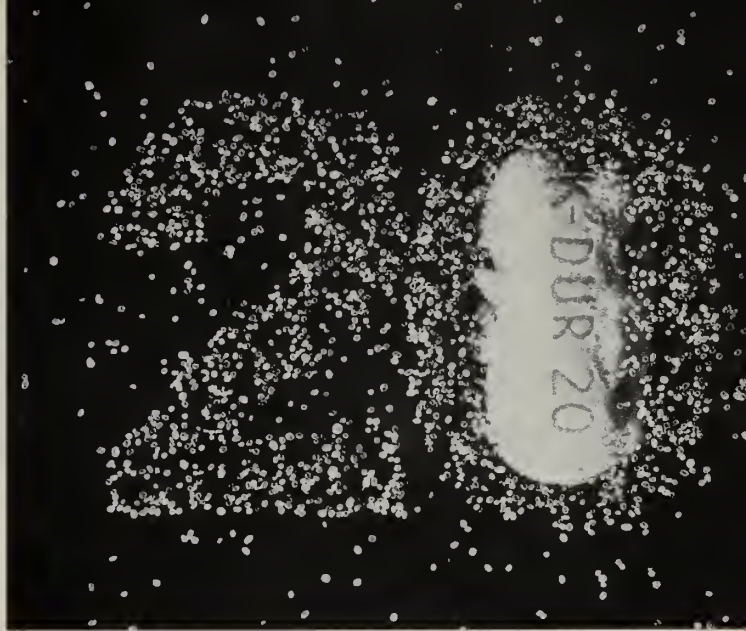
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K-DURTM Microburst Release System (potassium chloride) Sustained Release Tablets

INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1 For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2 For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions. Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3 The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics, see **WARNINGS**.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

- 1 Elimination of foods and medications containing potassium and of potassium-sparing diuretics
- 2 Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
- 3 Correction of acidosis, if present, with intravenous sodium bicarbonate
- 4 Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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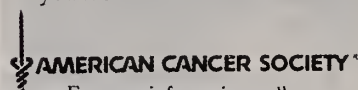


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Mirada a Nuestro Pasado - Hace 50 Años...

Extracción de la Catarata Senil por Medio de la Ventosa*

Luis J. Fernández, MD

La introducción de un aparato aspirador en el interior del globo ocular es cosa conocida desde el siglo diez, habiendo sido practicado por el árabe Ammar. Naturalmente que esto sería tratándose únicamente de cataratas blandas como en la congénita o en la traumática en los jóvenes. El primer conocimiento que tenemos de la extracción de la catarata dura a la ventosa se debe al alemán Stoeber en el año 1902: éste adaptó una cánula ventosa a una pera de goma con la cual hacía el vacío. Herz, de Viena, presentó una ventosa parecida; luego Vard Hulen, en San Francisco, California, presentó su aparato y técnica en 1910. En 1917 Ignacio Barraquer dio a conocer su método que es una modificación de los anteriores; él hizo experimentos sobre la elasticidad y fuerza necesaria para romper la zónula en un gran número de cadáveres, encontrando que en una persona de más de 40 años las fibras se estiran uno o dos mm. y se necesita una fuerza de 30 gramos para romperla. La fragilidad de la Zónula aumenta con la edad y con la madurez de la catarata, de modo que en los ancianos hasta 2 gramos de fuerza pueden romperla. Barraquer trató de diseñar un aparato en que se produjese un vacío vibratorio instantáneo de modo que al aplicarse a la catarata rompiese el ligamento en su inserción en el ecuador de la lente para de ese modo no perturbar el cuerpo ciliar, o la parte ciliar de la retina. Esto descansa en una conocida experiencia física.

Como Barraquer ha sido el más entusiasta promulgador de este método de extracción de la catarata, algunos le han dado su nombre. Su entusiasmo llegó al extremo de llamarle al aparato "Zonulótomo" y al método, el "ideal para la extracción de la catarata". Nosotros creemos que es física y anatómicamente imposible romper toda la zónula instantáneamente con la poca desfiguración que sufre la lente, excepto quizás en una catarata con zónula muy frágil, y la experiencia nos lo ha demostrado. En la mayoría de los casos, después de hacer presa la catarata, tenemos que mover la ventosa lateralmente para desprenderla un poco (y se siente la resistencia) antes de darle la vuelta con lo que se consigue romper todas las fibras. En algunos casos de zónula muy resistente esto no se consigue, la ventosa suelta o arranca un pedazo de la

cápsula. Tampoco creemos que esta operación sea la ideal como ninguna otra particular lo es. Ideal sería una operación de catarata aplicable a todos los casos y practicable por el operador promedio. Hasta ahora el método ideal es el aplicable al caso individual en la forma que mejor domine el operador.

Aparatos

El aparato que nosotros usamos es uno de los modelos de Barraquer consistente de un motor acoplado a una bomba rotatoria que trabaja en aceite produciendo un vacío vibratorio. Este se mide en un manómetro conectado por un tubo de gomas y otro tubo de goma conecta la cánula ventosa al manómetro. La cánula ventosa tiene en el mango una válvula que trasmite el vacío a la copa apretando un botón con el dedo pulgar. Este aparato tiene algunos inconvenientes; es costoso, requiere la ayuda de una persona entendida, requiere aplicarlo a corriente eléctrica, necesita un aceite especial, tubos de goma especiales, etc. Tiene la ventaja de que hay vacío continuo, de modo que si la ventosa desprende una vez, está lista para volver a intentar la presa de la catarata. Varios oculistas en diversas partes del mundo han hecho aparatitos pequeños, en los cuales el vacío se produce en el mango del instrumento por medio de un dispositivo metálico o de vidrio con un pistón que produce vacío para un agarre solamente. El primer tipo metálico lo presentaron unos franceses en el año 1934 y el tipo con mango de jeringa de vidrio creo que fue Agarañas, de Argentina quien primero lo ideó; de este tipo hay uno en el mercado norteamericano con el nombre de Dimitri.

Técnica Operatoria

En la operación extracapsular se abre el quiste y se saca su contenido, la operación intracapsular es luxar el quiste, o sea la lente ocular degenerada y exprimirla o extraerla, cápsula y contenido. En la extracción a la ventosa la catarata se arranca de su ligamento completa y se extrae completa. Puede ser ayudada la ventosa por medio de presión con gancho como en la extracción a pinzas, de modo que la ventosa es prácticamente una pinza neumática. Nosotros, no obstante, la usamos solamente en aquellas cataratas en que la pinza falla, es decir no hace presa de la cápsula, siendo la extracción a pinza y gancho más fácil y menos aparatosa. La anestesia como

en la extracción a la pinza tiene que ser perfecta, también la parálisis, o aquinesia del orbicular y de los músculos extrínsecos del ojo. Puede usarse el blefarostato para separar los párpados, pero nosotros usamos el cabo al recto superior y cabo al párpado inferior. El tallado del colgajo de 180° en el mismo limbo esclerocorneal, la sutura limboepiscleral y la iridectomía periférica hora 12, todo como en la extracción a la pinza. La ventosa se introduce levantando el colgajo con unas pinzas que tiene el operador en su mano izquierda; se aplica levemente sobre la cara interior del cristalino un poco más abajo del área pupilar hacia h. 5; se aprieta el botón del mango que conecta al vacío y la catarata queda instantáneamente presa a la ventosa. Luego se le dan movimientos laterales para romper el ligamento. La extracción puede efectuarse seguido en la posición en que está la catarata, levantando el mango del instrumento para franquear la pupila arriba y tirando hacia afuera; o como la prefiere Barraquer haciendo la versión, dando la vuelta al aparato, de modo que la catarata sale con la cara posterior hacia la córnea.

Las suturas se terminan como en la extracción a la pinza ya descrita.

La ventajas de la ventosa son: 1- Agarra cualquier catarata; 2- Hay menos riesgo de luxación posterior o pérdida de vítreo, pues para agarrar la lente no se hace presión sobre ella; 3- No hay opacidad post-operatoria de la córnea como en la extracción a pinza.

Condiciones que abonan al dominio de la técnica y éxito de la operación:

En cuanto al operador:

- 1- Conocimiento pleno de la anatomía del ojo.
- 2- Conocimiento perfecto del aparato que se usa.
- 3- Suficiente destreza manual natural.
- 4- Dominio de sus reflejos y de sus nervios.
- 5- Buena visión.

Es nuestra experiencia que el uso de una "telescope" como la de Zeiss es una gran ayuda, pues se obtiene un aumento de dos a una distancia conveniente de ocho pulgadas.

Por lo demás, es menester un instrumental apropiado y que los casos sean escogidos como de riesgo mínimo.

Nosotros podríamos decir que no operamos cataratas, operamos pacientes con ojos cataratosos. No seguimos una técnica estricta punto por punto; el procedimiento a seguir lo determinan el aspecto general del paciente y el aspecto local del ojo, antes y después de tallado el colgajo. Tratamos de rodear la operación de todas las seguridades posibles. El aspecto local determina si la catarata es o no operable.

Párpados desprovistos de erupciones, eczema, etc., conjuntiva normal, y muy particularmente vías lagrimales permeables. Uno o dos días antes de la operación dilatamos el canalículo inferior e inyectamos solución salina con una jeringuilla y cánula de vías lagrimales; el líquido deberá salir libremente por la nariz. Si la conjuntiva fuere de aspecto sospechoso hacemos cultivo de un frotis. El iris deberá ser normal con una pupila activa. Estudiamos la córnea en la lámpara de hendidura y microscopio para la presencia o ausencia de precipitados

queráticos. Investigamos la apariencia del cristalino y cápsula.

Luego examinamos la función retiniana. Demás está decir que examinamos detenidamente siempre ambos ojos. Si la opacidad no es completa dilatamos la pupila y examinamos el fondo ocular, puede aunque se vea con dificultad, podrían notarse lesiones grandes de la coriorretina.

En cuanto a la visión mínima que deberá tener un ojo para recomendarse operación, hay variación de opiniones. Los Green en San Francisco dicen que ellos operan un ojo con 5/10 de visión. Nosotros creemos que un ojo se debe operar cuando el paciente lo necesite según su vocación, es decir, un trabajador o profesional cuando ya no pueda ganarse la vida, cuando la visión esté en 3/20 ó menos con corrección. Otras personas pueden esperar más.

Cuando el caso se presenta con visión de bultos o menos; probamos la proyección luminosa y la percepción de colores; también la presencia de fosfenos, o sea, el fenómeno entóptico que resulta del estímulo mecánico de la retina normal.

Siempre probamos también la tensión intraocular.

En el aspecto general nos cuidamos de que no haya sífilis, infecciones focales, diabetes no atendidas, afecciones de las vías respiratorias, anemia, hipertensión arterial marcada, etc. Y siempre probamos el período de coagulación de la sangre. Mujeres que aún menstrúan deben operarse poco después de pasada una regla.

Antes de la operación determinamos si el caso puede o debe hacerse por el método intracapsular o extracapsular. Luego después de tallar el colgajo el estado de presión intraocular determina qué procedimiento a seguir. Se pueden dividir los ojos en tres clases según su grado de presión, después de tallado el colgajo:

1- *Presión negativa*: El vítreo parece estar contraído, el diafragma irido-lenticular está bajo y la córnea se colapsa. Este es el caso bueno para la ventosa. La pinza agarra la cápsula, ayudada por presión con el gancho abajo en la esclera, para aumentar la tensión interna.

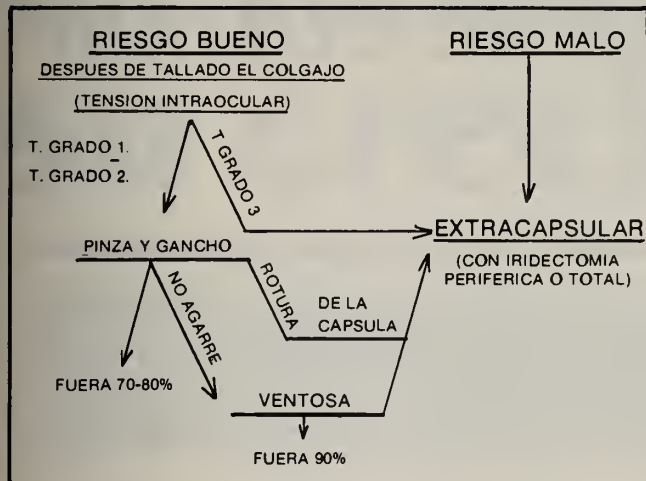
2- *Presión normal*: El vítreo ocupa aparentemente espacio un poco aumentado, el diafragma sube ligeramente, la córnea queda redonda, el iris no tiende a salir. Bueno para pinza y gancho.

3- *Presión positiva*: Seguido de tallado el colgajo y escaparse el humor acuoso, el diafragma irido-lenticular sube y hace presión contra la córnea, quedando el colgajo algo levantado produciendo pliegues transversales en la córnea, uniendo los extremos de la incisión; el iris tiende a salir y es difícil o imposible llevarle a su sitio; el vítreo se saldrá si se le da oportunidad. El procedimiento a seguir en estos casos es siempre: iridectomía completa y extracción extracapsular.

Las causas de presión positiva son:

- 1- Hemorragia retrobulbar.
- 2- Demasiada inyección retrobulbar.
- 3- Contracción del orbicular o de los músculos extrínsecos (akinesia y anestesia pobres).
- 4- Defectos en el saco conjuntival o los párpados.

Nuestro procedimiento operatorio se explica por el siguiente diagrama o esquema:



Operando sin apuro, dándose buena cuenta de las circunstancias, no arriesgándose nunca más de lo prudente, tomando todas las precauciones, y poniendo buenas suturas (dos profundas h. 1 y 11, y posiblemente tres suplementarias superficiales), las pérdidas de vítreo y las hernias del iris serán prácticamente suprimidas.

El cuidado post-operatorio es de suma importancia, pero no podemos describirlo aquí por estar fuera del alcance de este trabajo.

COMENTARIO

Extracción de la Catarata Senil por Medio de la Ventosa

Jaime E. Irizarry, MD

Es con placer que respondo al análisis del artículo por Dr. Luis J. Fernández titulado "Extracción de la Catarata Senil por Medio de la Ventosa", y publicado hace 50 años en nuestro Boletín.

El mencionado artículo resume, en forma muy acertada, el manejo quirúrgico de la catarata 50 años atrás. Resalta la aseveración del Dr. Fernández, donde resume la principal indicación para la operación de catarata: "Nosotros creemos que un ojo se debe operar cuando el paciente lo necesite según su vocación...". Esta sigue siendo, y siempre debiera ser, la indicación básica para esta operación.

La extracción del lente cristalino opacificado adelantó cuando se diseñó la ventosa descrita en el artículo, la cual se usó por muchos años. Menciona el Dr. Fernández el método usado por él para romper las fibras del ligamento zonular del lente y hacer posible la extracción intracapsular. Fue esta maniobra la que más problemas causaba en esta operación, dificultad que desapareció cuando el Dr. Barraquer en Barcelona, España, desarrolló en 1957, el uso de la enzima alfa-quimotripsina, que inyectada en la cámara posterior del ojo, disolvía las zónulas, facilitando la extracción del lente. La ventosa no perdió por esto su utilidad, continuándose su uso hasta que la extracción extracapsular de la catarata, mencionada por el Dr. Fernández, suplantó la intracapsular, con el advenimiento del uso extenso de lentes intraoculares. El Dr. Fernández presentó en su artículo una fase de cirugía oftálmica muy informativa y de actualidad para el tiempo en que se publicó.

Jefe, Servicio de Oftalmología, Hospital de Veteranos, San Juan, Puerto Rico.



CARTAS AL EDITOR

Educación Médica Continuada y la Práctica de la Medicina

Recientemente hemos leído en el *Boletín* sobre la controversia en torno a los programas de educación médica continuada y la excelencia en la misma.

El tema es sumamente interesante. En nuestra opinión, la medicina arranca de una contradicción: mientras más enfermos mayor debe ser nuestra preocupación. Pero no debemos aceptar que mientras más enfermos mayor debe de ser nuestro ingreso económico.

Puerto Rico es una isla muy pobre. Vivimos en un espejismo que ha conducido a crear una sociedad que nada tiene, (un 60%) frente al resto que todo le sobra. Puerto Rico no es los Estados Unidos de Norteamérica. Más bien es una isla pobrísima. No es Dinamarca, ni es Alemania ni es Inglaterra, países con un alto nivel económico y donde la medicina se encuentra socializada.

Favorecemos la socialización de la medicina, lo cual sería una especie de seguro universal de salud, como apuntara en su día la Senadora Melo Muñoz. El Estado ofrecería así, unos servicios de calidad, con suficientes especialistas y exigiría el pago de un canon modesto por esos servicios. Esos ingresos llevarían al Departamento de Salud a un estado de suficiencia y las poderosas casas privadas de seguro de enfermedad no controlarían la salud en la Isla.

Para mejorar la salud y la educación médica tenemos que practicar la libertad. Que nadie nos fíche por las ideas. Que no sea inconstitucional —como lo es hoy— el pensamiento médico en más de 3 veces. Que el pensamiento sea libre. Que no sea una docena de médicos quienes ordenen y pongan de rodillas a todo un pueblo en cuanto a la política pública de salud. La medicina debe estar en manos de aquellas personas con vocación y no con otros intereses.

Hay un chiste en cuanto a la supuesta tartamudez de Moisés. Resulta que parece ser que él no quería decir que la patria judía no era el Canaán sino el Canadá. Y que cuando habló sobre las tablas de la Ley, algunos “li\$to\$” —aduciendo a su tartamudez— expresaron que lo que Moisés afirmó fue la importancia de la tabla de multiplicar.

Cecilio Font, MD
San Sebastián, P.R.

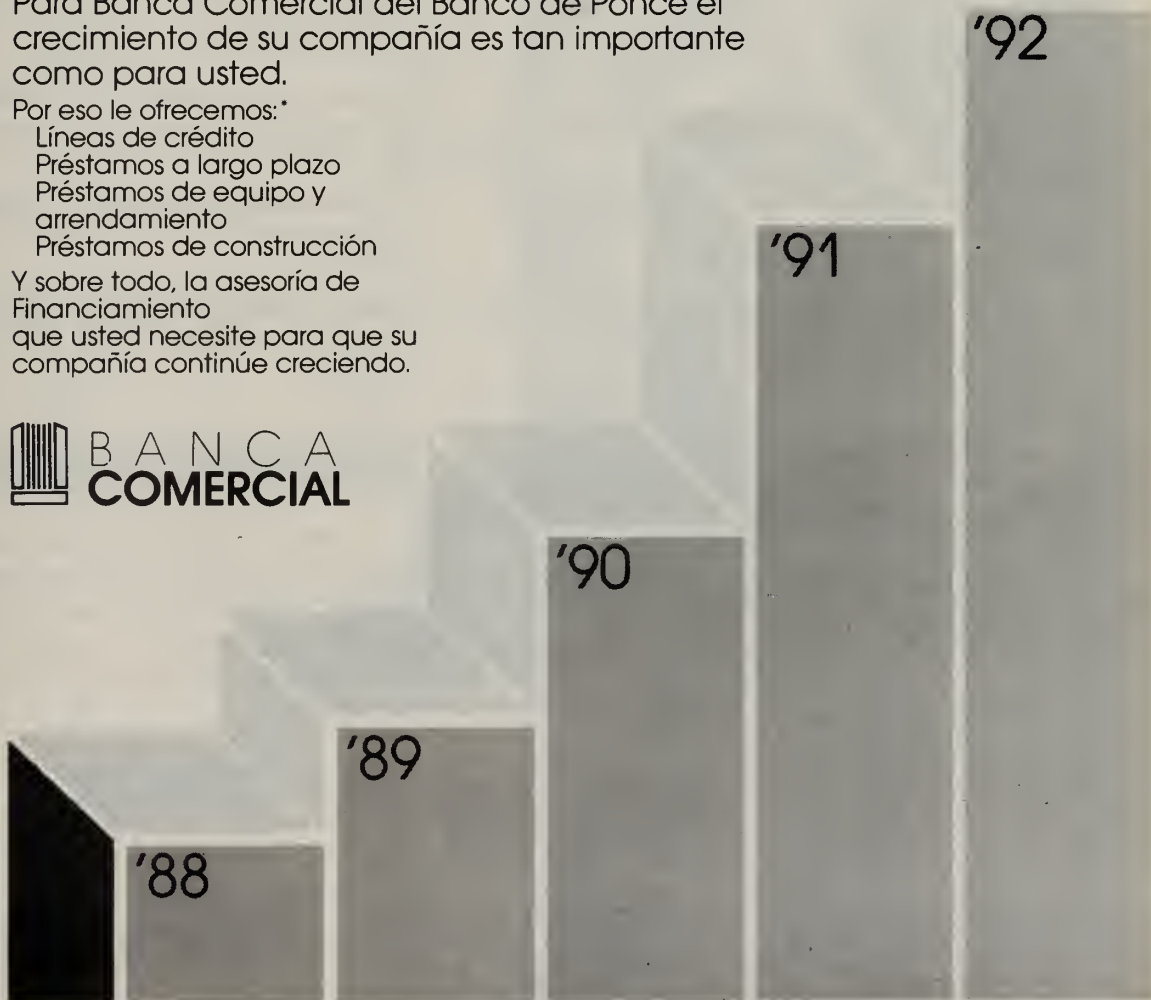
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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

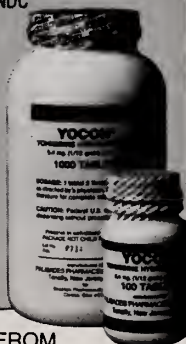
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr.: 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

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4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Collazo Bonilla, Angel L. MD - Escuela de Medicina de la Universidad de Zaragoza, España, 1976. Obstetricia y Ginecología. Ejerce en Bayamón.

Paz Fustes, José Ramón MD - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1980. Patología. Ejerce en Hato Rey.

Quevedo Bonilla, Gerardo MD - Escuela de Medicina de la Universidad de Puerto Rico, 1980. Cirugía. Ejerce en Bayamón.

Varela Fernández, Alberto MD - Escuela de Medicina de la Universidad de Puerto Rico, 1967. Psiquiatría. Ejerce en Cidra.

INTERNOS-RESIDENTES

Berrios Rivera, Jorge R. MD - Escuela de Medicina de la Universidad Central del Caribe, Cayey, 1984. Medicina Física y Rehabilitación.

Mendoza Rosa, Félix MD - Escuela de Medicina de la Universidad de Puerto Rico, 1984. Urología.

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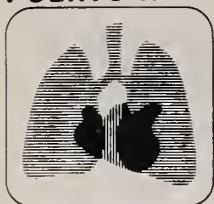
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AMERICAN ACADEMY OF PEDIATRICS

AAP OPPOSES MOST INVOLUNTARY DRUG SCREENING

The American Academy of Pediatrics (AAP) announced that it opposes involuntary drug testing for older, competent adolescents, and that permission from parents is not sufficient to screen this group for drugs without their approval.

In the case of drug screening for participation in school sports, student athletes should not be singled out for involuntary drug screening, according to the AAP policy statement, published in the March issue of *AAP News*. Except for health-related purposes, such testing should not be a condition for participation in sports or any school function.

"If the primary purpose of drug screening was health promotion, there would be little reason for singling out student athletes, as the use of illicit drugs, alcohol and tobacco are prevalent throughout the adolescent population," the AAP says.

The statement—a collaborative effort between the AAP's Committees on Adolescence, Bioethics and Substance Abuse—also notes that voluntary screening for drug treatment is ethical, but the psychosocial risks of this warrant careful attention to informed consent and confidentiality. "Voluntary" screening may be a deceptive term in that there are often consequences for those who decline to volunteer.

The AAP urges pediatricians to counsel and treat adolescents who use drugs, not do "police work." AAP President Donald W. Schiff, M.D. notes that pediatricians shouldn't perform drug screening for the primary purpose of detecting illegal use.

The older, competent adolescent's consent, however, may be waived when there is reason to doubt competency or where the youth's history and physical exam suggest

high risk of serious damage due to substance abuse.

Dr. Schiff says that parental consent may be sufficient for involuntary screening of younger children. "Minors have a diminished capacity to make informed, autonomous decisions," he explains.

Reasons for Drug Screening

Two primary reasons for involuntary drug screening are identification of candidates for treatment and identification of wrong-doers for purposes of punishment.

"There is no objection *per se* to screening, with appropriate consent, for purposes of identification and treatment," writes the Academy. "If a specific individual is suspected of criminal behavior, the police should obtain the necessary authority to search and/or screen for drug use."

In addition, the AAP says that screening under any circumstances—voluntary or involuntary—is improper if there is not reasonable certainty that the results are accurate. "Because the consequences of inaccurate results can have profound implications, it is especially important that physicians be assured of the reliability of the testing in its entirety."

The Academy condemns the nontherapeutic use of psychoactive drugs by children and adolescents.

FEAR OF OBESITY HAUNTS ADOLESCENT GIRLS

A recent study confirmed that adolescent girls are afraid of becoming obese and their unrealistic ideas can influence their actual weight.

The study, published in the March issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), reported that "fears of obesity" were common in the 326 high school girls surveyed regardless of whether they were overweight, normal weight or underweight. "Fear of obesity and inappropriate eating behaviors are pervasive among adolescent girls regardless of body weight or nutrition knowledge," the study said.

The study encouraged pediatricians to be aware of this situation, for it may be associated with many medical problems such as poor growth.

The girls were students at an all-girls Catholic high school in an upper-middle class suburb of Long Island, N.Y. Among the under weight girls, as many as 51 percent reported extreme anxiety about weighing too much, and 36 percent said they were preoccupied with body fat. Their peers who were normal weight or overweight expressed these concerns even more frequently.

"The distorted perceptions of ideal body weight appeared to influence the student's actual body weight. Those who perceived a low ideal body weight did indeed have a reduced weight," reported the researchers.

According to Fima Lifshitz, M.D., Professor of Pediatrics, and his collaborators at North Shore University Hospital-Cornell University Medical College,

Manhasset, N.Y., the girls' fears of becoming obese often were expressed through increased dieting and frequent weighing. They found that 72 percent of the girls dieted and 55 percent weighed themselves at least every other week. The remaining 45 percent weighed even more frequently, including 18 percent who weighed themselves once a day, and 4 percent who weighed in more than once a day.

The researchers attributed the girls' preoccupation with weight to social pressure.

"This problem of fear of fear of obesity appears to be deeply ingrained in our society as a result of the cultural preoccupation with obesity and the value placed on being slim," they wrote. "Television, magazines and even the classroom promote the goal of thinness with regard to both beauty and health.

"This social phenomenon has an impact not only on adult and adolescent eating habits but may also influence the eating habits of young children. Concepts regarding body weight and appearance are formed very early in life. In fact, elementary school children have been shown to perceive obesity as being worse than being handicapped or disabled."

General knowledge of nutrition did not seem to positively influence the attitudes or eating behaviors of the girls, the study found.

In addition to answering questions about their perceptions of weight, their eating behaviors and their nutritional knowledge, the girls were weighed and measured. Their measurements were then compared to growth standards established by the National Center for Health Statistics to determine whether the students were underweight, normal weight or overweight.



NEW ALTERNATIVES CITED IN SUPRAVENTRICULAR TACHYARRHYTHMIAS

New information on the diagnosis and therapy of supraventricular tachyarrhythmias was presented by Dennis L. Kuchar, M.D. and colleagues at the Massachusetts General Hospital, Boston, comparing the predictive value of the delta wave during sinus rhythm and P wave morphology during tachycardia for localization of bypass tracts in 51 patients with pre-excitation and orthodromic tachycardias who underwent EPS. P-wave polarity was reasonably specific: when upright in a VL, a left lateral tract was likely; upright in lead III, a right-sided tract was likely; and upright in V4, a septal tract could be diagnosed. But sensitivity at these sites was low: only 35% of patients with left lateral tracts had upright P wave in lead a VL, for example. Delta wave

polarity did better with sensitivities from 67 to 83% and specificities of greater than 90%. A negative or isoelectric delta wave in a VL predicted a left lateral bypass tract; in lead III, a posterior tract; and in lead a VR or V1, an anteroseptal tract.

Flecainide and Sinus Rhythm

I.V. Gelder and the group at University Hospital, Groningen, The Netherlands, studied the efficacy of flecainide in maintaining sinus rhythm after d.c. cardioversion of chronic atrial fibrillation (AF) or flutter in a randomized trial. After 12-month follow-up, there was a significantly higher relapse rate in the placebo group (96%) compared to the flecainide group (65%). Side effects were infrequent.

"Stepped Care" Approach

In refractory AF, antiarrhythmic treatment may be cumbersome. Elliott M. Antman, M.D., et al of the Brigham and Women's Hospital and Harvard Medical School, Boston, presented data on 74 patients treated with a "stepped care" approach to this problem. The patients were 64% male, had a mean age of 62 years, a mean LA size of 45 mm, and a mean LVEF of 54%. Most patients had failed two prior drug regimens. They were treated sequentially with propafenone (Rhythmol™ Knoll), a IC antiarrhythmic expected to be made available shortly, at a dose of 450-900 mg/d; sotalol, 160-900 mg/d; amiodarone then maintenance of 200 mg/d; or amiodarone plus propafenone.

Treatment was advanced one stage when AF recurred or intolerable drug toxicity was noted. Based on life table analysis, the cumulative percentage of patients free of AF at six months was 41% for those treated with propafenone alone; 72% of those advancing to sotalol; 76% of those advancing to amiodarone; and 76% of those requiring both. Thus, most refractory patients can be maintained on regimens that do not require amiodarone.

UPDATE ON CARDIAC TRANSPLANTATION

Coronary Artery Disease After Transplantation

Investigators at the University of Minnesota reported on 74 patients followed after transplantation with annual angiography. Nearly all were hypertensive; all were treated with cyclosporine, prednisone and azathioprine. One-year and 3-year survival rates were 95% and 90% and the probability of acute rejection was 10.8% at 1 year. The incidence of CAD was 5% at one year, 24% at two years and 44% at three years, though only 18 patients had followup for that length of time. There was no correlation between CAD and HLA type, age, sex, diabetes, cholesterol or smoking. In another presentation, the Stanford group compared immunosuppression with cyclosporine and azathioprine and found no difference between them with respect to the incidence of CAD at seven years. And, in a presentation by George Petrossian, M.D., of Columbia University, New York, the presence of anti-HLA lymphocytotoxic antibodies

was associated with higher mortality and a higher incidence of CAD. Such antibodies were present in 11 of 81 patients with CAD and 1 of 42 without (14% vs. 2%, $p < 0.05$)

How Old Can the Donor Be?

With an increasing demand for donor hearts, increasing the pool by extending the age limit is an enticing idea. The German Heart Institute in Berlin began accepting donors up to age 50, generally without preoperative angiography, and presented their results. Compared to the 117 donors under age 35 the 60 patients who received a heart from a donor 35 to 50-years-old had no significant differences in early graft failure, late LVEF, or graft atherosclerosis. And, at several institutions in Houston, 15% of their 314 donors were over age 35. They found no greater incidence of CAD and survival rates were similar.

Treatment of Acute Rejection

A novel idea emerged from the University of Arizona at Tucson: taking advantage of ketoconazole's effect on inhibiting cyclosporine metabolism in the liver. This resulted in a mean 88% lowering of the daily cyclosporine dose, and lower mean BP. Renal function was similar in those treated with and those without ketoconazole. The projected savings as nearly \$4000 per year per patient. A retrospective comparison of oral and intravenous steroids for acute rejection was undertaken at Temple University. Investigators found that oral steroids were less costly, had fewer side effects and were comparable or greater in efficacy; a prospective trial is warranted. At Stanford University, workers used OKT3, a monoclonal antibody against T lymphocytes, as an immunosuppressive, findings a similar efficacy, reduced rejection, shorter hospital stay and reduced cyclosporine dosage and less renal dysfunction. The antibody was added to the traditional regimen of cyclosporine, azathioprine, prednisone and antithymocyte globulin.

Using Echocardiography to Detect Rejection

Also at Stanford, Doppler indices of LV fillings were used to screen for acute rejection. A 15% decrease in isovolumic relaxation time or mitral pressure half-time or a 20% increase in peak early mitral flow velocity were considered indicative of acute rejection with myocyte necrosis. In 12 patients randomized to be followed this way, results were compared to periodic biopsies. If Doppler criteria were used, 1 to 9 episodes of rejection would have been missed, two negative biopsies would have been performed, and 60 routine biopsies could have been avoided. This and other newer, noninvasive modalities for rejection diagnosis (such as Indium-111 labelled monoclonal antimyosin F(ab) with tomographic imaging) are likely to come into widespread use, if these results can be confirmed.

COCAINE AND THE HEART: THE EPIDEMIC CONTINUES

Most inner city hospitals see cocaine-related cardiac illnesses on a regular basis. Despite the growing clinical

information, only recently has basic science caught up with the epidemic. Some new information came from the recent American Heart Association meeting.

Investigators from the University of Medicine and Dentistry of New Jersey, Newark, led by R. Patel, M.D., studied 18 patients who sustained MIs temporally-related to cocaine use. Thirteen underwent coronary angiography; 11 had an occluded infarct-related artery, nine of which had arteriographic characteristics of a thrombus in the absence of atherosclerosis. Autopsies performed in three other patients demonstrated intracoronary thrombi in two. There was a predilection for the LAD (89% of cases). Of note, all patients were smokers.

Effects of Smoking and Caffeine

Workers at Harvard Medical School showed that caffeine, in concentrations found in the American diet, potentiates the *in vitro* adrenergic effects of cocaine so that smoking and caffeine may be risk factors for cocaine-induced disease. Also in an *in vitro* model, Anthony J. Rongione and associates from Tufts University School of Medicine, Boston, demonstrated that cocaine has a vasoconstrictor effect on vascular smooth muscle which is independent of the endothelium. And, in three papers from Georgetown University, workers demonstrated that the coronary vasoconstrictor effect of cocaine is mediated by norepinephrine activation of alpha-1 receptors. Further, the adverse cardiovascular effects are shared by a cocaine derivative which does not cross the blood-brain barrier, so that participation by the central nervous system does not seem to be required for adrenergic hyperactivity.

The Mechanism

N. Hague et al, of Harvard Medical School, Boston, demonstrated that cocaine causes a direct alteration in intracellular calcium handling. This, coupled with the electrophysiologic data of Tove S. Rosen et al of Columbia University, New York, could explain the spectrum of adverse cardiac effects, including local anesthetic properties, positive inotropic effects in low doses and negative inotropic effects in high doses.

SURGICAL AND MECHANICAL THERAPY OF CONGESTIVE HEART FAILURE

The Hemopump, the Jarvik Total Artificial Heart and cardiomyoplasty were all discussed as potential treatment modalities for severe heart failure at the AHA meeting in Washington, D.C.

The Hemopump

The Hemopump is an axial flow left ventricular assist device which is placed percutaneously, retrograde across the aortic valve. It can provide up to 3.5 L/min of non-pulsatile output, and experimental work at the University of Texas and Athens University demonstrated its utility. At the former site, the Hemopump resulted in reduced systolic pressure and LVEDP with increased aortic pressure in a dog model of a left anterior descending artery

occlusion. Wall motion improved in the ischemic zone as well. At the latter site, a combination of an intra-ventricular balloon and intraaortic balloon pumps provided circulatory support in animals and was suggested as a possible "bridge-to-transplantation" device.

Jarvik Total Artificial Heart

The Jarvik Models 7 and 7-70 experience was reviewed by groups from Pittsburgh and Minneapolis. Of 100 patients in a multicenter study who underwent implantation, 70 ultimately went to transplantation. The 30-day survival was 77% in this group and the long-term survival, 54%. There was a 9% incidence of CNS thromboemboli. In the Pittsburgh experience with 12 patients, major complications occurred in five patients prior to transplantation, precluding a successful outcome.

Cardiomyoplasty

Is there a potential for surgery in the patient with CHF? The dynamic cardiomyoplasty, an operation developed in France in which a latissimus dorsi muscle flap is wrapped around the heart, appears to offer promise. From Paris, the group of Alain F. Carpentier, M.D., reported on their results in three patients. Though there was obvious clinical improvement, LVEDP remained high and LV volumes enlarged and improvement in EF was variable. At the University Hospital, London, Ontario, augmentation of RV systole was documented in a dog model, and at McGill University, Toronto, the growth potential of the muscle flap was demonstrated, suggesting that the operation could be used in pediatric patients as well.

PROMISING RESULTS FOR THE USE OF FLECAINIDE AND ENCAINIDE IN SUPRAVENTRICULAR ARRHYTHMIAS

Two of the more recently introduced antiarrhythmic agents, encainide and flecainide, have proven invaluable in the management of patients with ventricular arrhythmias. Classified as Vaughan-Williams type IC drugs, both are potent sodium-channel blockers which markedly depress conduction. They also prolong repolarization, but to a lesser degree. As experience with these agents grows, newer uses (not currently FDA-approved) are forthcoming. One such use is in patients with supraventricular tachycardias (SVT).

SVT includes sinus tachycardia, atrial flutter, atrial fibrillation, AV nodal tachycardias and circus movement tachycardias which utilize accessory pathways. Data has appeared on the role of encainide in AV nodal tachycardias and in bypass tract, and on the role of flecainide in these as well as in atrial fibrillation. Though flecainide is more of a negative inotrope, the electrophysiologic properties of these two agents are quite similar and for most patients with SVT, they may prove to be interchangeable.

Encainide Studies

M.L. Markel and coworkers at the Indiana University

School of Medicine, studied the role of encainide in 33 drug-resistant patients with SVT, associated with the Wolff-Parkinson-White (WPW) syndrome, who were treated for a mean of 26 months. Palpitations were abolished or markedly decreased in 73% of patients. Adverse effects required discontinuation of medication in only two patients (6%). No patient had syncope or required cardioversion but one had ventricular tachycardia. Efficacy was similarly high in patients with atrial fibrillation. Electrophysiologic study (EPS) demonstrated that the mechanism of the effect was generally development of antegrade block in the accessory pathway. Prolongation of atrial and ventricular refractory periods and retrograde block in the bypass tract were also demonstrated. Induction of AV nodal tachycardia was prevented in 36% of patients at EPS and was associated with loss of delta waves from the surface ECG during encainide therapy. The authors concluded that "oral encainide is a well-tolerated form of chronic therapy for patients with SVT associated with WPW syndrome."

In another group of 11 patients treated by H.J.J. Wellens and P. Brugada in The Netherlands, oral encainide prevented clinical recurrence of drug-refractory SVT (atrial in two, bypass tract in nine) in seven cases over a followup period averaging 11 months. The likely mechanism, based on EPS, was prevention of the tachycardia-initiating premature beat, since inducibility at EPS was not very predictive of clinical efficacy.

Flecainide Proven Effective

Flecainide was proven effective in 15 patients with drug-resistant bypass tract tachycardias in a study reported by Zee-Cheng and workers at Washington University, St. Louis. One patient was intolerant to the drug and five had recurrences which prompted during a mean followup interval of 18 months. In 14 drug-refractory patients whose tachycardias were complicated by atrial fibrillation or flutter, seven had successful long-term (mean, 21 month) treatment with flecainide. Two proarrhythmic events were noted in patients with advanced structural heart disease.

As prophylaxis for atrial for atrial fibrillation, flecainide was studied in 40 patients in France by Chouty and Coumel.

All were resistant to other antiarrhythmics, including high-dose amiodarone. Flecainide alone controlled the AF in 11 patients; when combined with amiodarone, 21 additional patients achieved control.

Conclusion

In reviewing a total of 80 papers, J.L. Anderson et al of the University of Utah reported on efficacy and safety of flecainide on data on nearly 1300 patients. Efficacy for conversion and maintenance of reentrant tachycardia control was about 75% and for bypass tract tachycardias and atrial fibrillation/flutter, about 60%. Paresthesias occurred in 7% of patients at risk and visual disturbances, 3%; proarrhythmias was seen in 4% of cases, conduction disturbances in 2% and heart failure in less than 1%. In discussing these results, Dr. Hein Wellens of Maastricht,

The Netherlands commented, "I think at this point in time, flecainide is an excellent choice for the treatment of WPW patients and AV nodal tachycardia." More data and eventual FDA sanction of this indication for type IC drugs are likely to appear in the near future.

NEW FORM OF NIACIN NOW AVAILABLE FOR HYPERCHOLESTEROLEMIA

Nicotinic acid (Niacin), an essential B-vitamin, has long been used for its ability to lower serum cholesterol in pharmacologic doses. Patient acceptance, though, has been less than optimal due to nuisance side effects. A new form, Slo-Niacin™ (Upsher-Smith), is now available in 250, 500, and 750 mg controlled-release, scored tablets, and has a more favorable side effect profile and greater patient acceptance.

Decreases Cholesterol

Niacin lowers total and LDL-cholesterol and triglycerides, and raises HDL-cholesterol through its effect on reducing hepatic VLDL production. In the Coronary Drug Project, it was associated with a lower incidence of recurrent myocardial infarction and lower total mortality. Both the decrease in total cholesterol (up to 25% in some patients) and the increase in HDL may be important in mediating its cardioprotective effects.

Side Effects and Restrictions

Facial flushing is the most common side effect, particularly when the drug is administered on an empty stomach. Even with the use of aspirin or other prostaglandin inhibitors, building up the dose gradually and optimal patient education, side effects occur—hence the usefulness of the slow-release preparation. The usual dose is 250 mg twice daily with meals, building up gradually to a dose of 750 mg twice daily. The scored tablets can be broken in half without the loss of the controlled release effect. The matrix is non-absorbable and may be excreted intact in the stool. If the hypolipidemic response is not satisfactory, the dose can be raised to a total of 3 g/day. A few patients may require up to 6 g/day to achieve an optimal cholesterol-lowering effect.

Because of the flushing, some patients with severe CAD may tolerate the drug poorly. It should not be given to patients with peptic ulcer disease, gouty arthritis or significant hyperuricemia, liver disease, arterial bleeding, severe diabetes or to pregnant women. Hyperglycemia, skin dryness, and mild gastrointestinal irritation may also occur. Liver function, glucose and uric acid should be monitored when therapy is initiated.

ROLE OF ARRHYTHMIAS IN CONGESTIVE HEART FAILURE QUESTIONED

Though 90% of patients with congestive heart failure (CHF) have ventricular arrhythmias and some 60-75%

have nonsustained ventricular tachycardia (VT), the need for and best form of antiarrhythmic therapy have not been firmly established. Two reports from the Vasodilator Heart Failure Trial (V-HeFT) have shed light on this topic. Jay N. Cohn, M.D. and associates, reporting for the VA Cooperative Group, reviewed 283 deaths in the 642 patients with DHF, enrolled in V-HeFT and followed for a mean of 2.3 years. Deaths were extensively investigated and classified as sudden (proven to be or presumably arrhythmic) related to pump failure, or various other causes. In the three treatment arms (placebo, prazosin or hydralazine/isosorbide dinitrate), the mechanisms of death were similar: sudden, approximately 44% of cases and pump failure, approximately 32%. Baseline LVEF, exercise performance and arrhythmias on Holter monitoring were not predictive of the mechanism of death. Vasodilator treatment reduced all-cause cardiac mortality.

Vasodilator Therapy

In an accompanying presentation, R. Fletcher, M.D. and V-HeFT collaborators attempted to determine the role of ventricular arrhythmias on the efficacy of vasodilator therapy. Holter tapes of 3-8 hours duration were obtained in 524 enrollees and patients were segregated as having or lacking runs of nonsustained VT (> 3 beats). The annual mortality rate was much higher in the placebo and prazosin groups if runs of VT were present. When the effective vasodilator regimen was used, the mortality was independent of the presence of VT. Mortality in this latter group, even with VT, was similar to placebo-treated patients without runs of VT. The authors noted that without runs to VT on the baseline Holter, there was no difference in annual mortality rate between the treatment arms—the benefit of the vasodilators being confirmed to the patients with ventricular arrhythmias. Further, the improvement with the vasodilator was independent of LVEF and of results of post-treatment Holters.

The controversy over antiarrhythmic therapy continues. Adding to it was a prospective, randomized double-blind trial of placebo vs. low-dose amiodarone in patients with severe CHF and low class II-IV ventricular ectopy. Patients had LVEF < 30% and dyspnea at rest or with minimal exertion and were randomized to placebo or amiodarone (1 month at 400 mg/d, then 200 mg/d). At a mean followup of nearly a year, side effects were rare but mortality and the incidence of sudden death were similar in the two groups. One-year survival was 75% in the amiodarone group and 72% in the placebo group. Neither LVEF nor parameters of the ventricular ectopy predicted overall survival or sudden death. It is evident that further investigation will be required before subgroups likely to benefit from amiodarone—the most effective antiarrhythmic in lethal or potentially lethal situations—or other antiarrhythmics can be defined.



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Reduce la hipertrofia⁶ ventricular izquierda y no afecta a los lípidos séricos desfavorablemente.^{2,5,11}

*Por favor, lea en la proxima página, la seccion de efectos secundarios en el resumen informativo para recetar.

90 mg SR bid

CSRAD817
0936A9

Dosis inicial



90 mg bid*

**Disponible también:
Cápsulas de 120 mg**

*La dosis debe ajustarse a la necesidad de cada paciente, empezando con 60 a 120 mg, dos veces al día.

EL NUEVO CARDIZEM[®] SR (diltiazem HCl) cápsulas de liberación sostenida

Para la hipertensión



CONTRIBUYENDO AL LOGRO DE LOS CUATRO OBJETIVOS¹ DE LA TERAPEUTICA ANTIHIPERTENSIVA

BRIEF SUMMARY CARDIZEM[®] SR (diltiazem hydrochloride) Sustained Release Capsules CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacological studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment,

may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use of CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) have been observed in angina trials. In many cases, the relation to drug uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SC and LOH (see hepatic warnings), vomiting, weight increase, thirst.

Dermatological: Patches, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturnal osteoarthritis pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/

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CAUTION URGED IN SCREENING AND TREATING SILENT ISCHEMIA

A commentary in the *Journal of the American Medical Association* cautions against rushing into the screening and treatment of patients with silent ischemia, or insufficient blood supply to the heart muscle.

Although they appear in good health and have no symptoms, persons with silent ischemia have narrowing of arteries that supply the muscle of the heart with blood. While some authorities recommend that people be screened for silent ischemia and that constricted arteries be widened by angioplasty or replaced by surgery, the commentary's author, Thomas B. Graboys, MD, of the Harvard School of Public Health, Boston, argues against this aggressive approach. Studies that have examined the procedures' safety and effectiveness to date have involved selected patients with known coronary artery disease, and not symptomless patients. "At present, there are no data on which to base a management approach for the true silent ischemic," he writes.

Graboys criticizes what he says are aggressive advertisements of drug and medical equipment companies that advocate screening and treatment regardless of symptoms. He cites a number of examples that he says are aimed at creating an enormous market for these products out of the millions of persons in the United States believed to have silent ischemia.

He also cautions against overzealousness in the quest for patients for these highly invasive procedures. "In the face of the cardiological 'gridlock' caused by the abundance of interventionists and the scarcity of patients with unstable angina, clinicians in some locales must take an almost entrepreneurial approach," he writes. "In the search for patients, the population of asymptomatic individuals with silent ischemia is becoming a suitable pool from which to draw."

Graboys warns against what he says are economically motivated special-interest groups that "create a seemingly hostile environment for the practitioner who hopes to maintain a conservative and noninterventional posture... Knowing that it is not in the best fiscal interest of either

hospitals or industry to curtail such interventions, one can only speculate whether studies that will address the issue of optimal management for the population base with so-called silent ischemia will ever be conducted," he concludes.

An accompanying report in *JAMA* examines another controversial issue in heart disease —the risks and benefits of treating heart attack patients with the thrombolytic drugs streptokinase and tissue-type plasminogen activator (TPA). Except for patients at special risk for cerebral hemorrhages, the benefits of these anti-clotting agents clearly outweigh any bleeding danger associated with these drugs, write the authors, Alan J. Tiefenbrunn, MD, and Philip A. Ludbrook, MB, BS, FRACP, of Washington University School of Medicine, St. Louis.

Based on a review of thrombolytic studies, they report that the mortality attributable to stroke in patients receiving anti-clotting agents was similar to the incidence of stroke-related deaths in controls. "Categorical refusal to utilize thrombolytic agents because of fear of potential hemorrhagic complications would be inappropriate, although vigorous patient selection designed to exclude patients with manifestations of cerebral vascular disease is essential," they conclude. "The potential benefits of prompt administration of thrombolytic agents are indisputable. The risk of obviating these benefits by failure to treat appropriate candidates clearly exceeds the risk of therapy."

JAMA April 14, 1989

THE SURVIVAL BENEFITS OF CORONARY ARTERY BYPASS SURGERY

For most coronary heart disease patients, coronary artery bypass graft (CABG) surgery now appears to offer significantly longer survival than medical treatment, a study in the *Journal of the American Medical Association* indicates.

Surgical survival progressively improved over the study period, from 1969 through 1984, and, in the study's last year, surgery was significantly better in terms of outcome than medical therapy for most heart patients, report the authors, Robert M. Califf, MD, and colleagues at Duke University Medical Center, Durham, N.C.

The degree of benefit does not depend on specific factors alone, such as age, severity of angina and degree of heart dysfunction, but apply across the spectrum of all patients with coronary disease, the authors write. "We found no evidence that the effects of CABG on survival were qualitatively different in different patient subgroups," they say. However, patients who benefited most were those with more severe coronary disease, those who had the worst prognosis, or those who were operated on more recently. The latter association is probably the

results of improvements in surgical and medical procedures in recent years, improvements which the authors believe are probably characteristic of most medical centers in the United States.

The expected one-year survival for the average surgically treated heart patients improved from 84 percent, in 1970 through 1971, to 95 percent in 1984, say the authors. Similarly five-year survival has improved from 76 percent, for patients undergoing surgery in 1970 through 1971, to 89 percent for those having surgery in 1980 through 1981. The authors attribute this improvement to better operative techniques, anesthesia, and patient support, especially in intensive care practices.

These findings are based on a study of 5,809 patients who received either medical or surgical treatment for coronary artery disease at Duke Medical Center. During the study period, 2,847 patients were treated medically and 2,962 underwent CABG surgery to replace narrowed arteries, which restricted the flow of blood to their heart muscles and increased the risk of heart attack.

"The decision to use CABG to treat a patient with coronary disease is complex and requires the integration of multiple factors in addition to the expected improvement in survival. While most patients with significant coronary disease have measurable survival benefits associated with CABG, large survival benefits are generally seen only in patients with extensive coronary disease and a high baseline medical risk (e.g. older age, severe or unstable angina, or reduced left ventricular function)."

The authors note, however, that the improvement in outcome due to surgical improvements is "probably characteristic of most centers in the United States and suggests that rigid application of therapeutic principles derived from the older data to clinical decision-making a decade later may not be warranted."

This view is emphasized in an accompanying editorial, by J. Willis Hurst, MD, of Emory University School of Medicine, Atlanta. "Whenever a study designed to compare the value of two types of treatment requires a 5- to 7-year follow-up to arrive at a conclusion, it is highly likely that each of the treatment modalities will improve as the years pass," he writes. "The therapeutic dilemma we face today is different from the problem addressed in the Duke study. The therapeutic problem now is to determine which patients who were formerly subjected to bypass surgery are candidates for coronary angioplasty." In coronary angioplasty, the narrowed heart arteries are widened rather than surgically replaced.

Though he agrees with the Duke investigators' conclusions regarding the value of bypass surgery compared with medical management, Hurst says "we must now consider the indications for coronary angioplasty. If the improvement in surgical technique played a significant role in improving the long-term result of patients having bypass surgery, one can predict that the technique of coronary angioplasty, including a decrease in restenosis, will improve as the years pass."

A related report in *JAMA* discusses factors that should be considered in selecting patients for percutaneous transluminal coronary angioplasty (PTCA). In this procedure, a balloon on a catheter is inserted into an

artery in the patient's arm or leg and is snaked up to the heart and into the affected coronary artery, where it is inflated to widen the narrowed section.

Current selection criteria include involvement of single or multiple coronary arteries, stable and unstable angina, and acute infarction, say the authors, David R. Holmes, Jr., MD, and Ronald E. Vlietstra, MB, ChB, of the Mayo Clinic, Rochester, Minn. "In the patient with moderate or severe angina and an ideal single-vessel lesion, PTCA now is accepted as the treatment of choice" in medical centers experienced with the procedure. Their findings are based largely on clinical experience rather than the results of randomized trials, they note. Currently, there is a multicenter trial comparing PTCA with medical therapy.

With ideal lesions, success rates should be greater than 90 percent, with low morbidity and mortality, the authors say. With more severe and diffuse coronary artery disease affecting multiple blood vessels, success rates are lower and complication rates are higher. If PTCA will not widen all severely narrowed arteries that supply blood to viable heart muscles, then CABG generally is preferable.

Among the issues that remain unresolved is whether PTCA may be superior than CABG surgery, how to prevent restenosis, which occurs in approximately 25 to 30 percent of treated lesions, and how best to organize the training and certification of specialists to maintain high standards of care, the authors conclude.

JAMA April 14, 1989

BETA-BLOCKERS MAY PREVENT FIRST HEART ATTACK IN HYPERTENSION PATIENTS

Beta-blocking drugs used to treat hypertension may also prevent first, non-fatal heart attacks in patients with high blood pressure, a study in the *Journal of the American Medical Association* concludes. The report, by Bruce M. Psaty, MD, PhD, of the Harborview Medical Center and the University of Washington, Seattle, and colleagues, involved a population-based, case-control study, with subjects gleaned from a large health maintenance organization. The 248 cases were hypertension patients who were treated with medication and suffered from angina or fatal or non-fatal heart attacks from 1982 to 1984. The 737 controls were a sample of HMO patients whose hypertension was treated with drugs but who were free of coronary disease. The researchers, blinded as to case or control status, reviewed subjects' medical records and found that "use of beta-blockers... was significantly lower in the cases than in the controls; this difference was confined to those with non-fatal infarctions." Those taking beta-blockers had a 38 percent lower risk of non-fatal heart attacks than hypertension patients whose treatment did not include such drugs. What's more, the authors note, "higher doses of beta-blockers conferred greater protection."

JAMA April 14, 1989

CYCLOSPORINE AND PSORIASIS, PSORIATRIC ARTHRITIS

Short-term, low-dose treatment with the immunosuppressant cyclosporine may help to treat both psoriasis and the associated arthritis seen in significant numbers of patients, a small study in April's *Archives of Dermatology* suggests. The report, by Aditya K. Gupta, MD, FRCP(C), and colleagues at the University of Michigan Medical Center, Ann Arbor, involved six patients with moderately severe to severe psoriasis who were given oral cyclosporine for eight weeks in an open study. Significant improvement in psoriasis was noted in all patients within two to four weeks, the authors say. In addition, at the end of the trial, the patients showed improvement in a number of measures of psoriatic arthritis. "Larger, double-blind studies will be required to confirm these preliminary findings and to determine the relationship of therapeutic benefit to toxicity," the authors say. Commenting editorially, Robert S. Stern, MD, of Beth Israel Hospital, Boston, urges caution in embracing cyclosporine as a psoriasis therapy, not its treatment role is not yet established. "Cyclosporine's use (in psoriasis) should be severely limited until the proper studies are completed, and it should only be dispensed by physicians expert in psoriasis therapy and knowledgeable about the proper use and monitoring of this drug."

WORLDWIDE PUSH URGED TO ELIMINATE HEPATITIS B

Accumulating data indicate that hepatitis B virus (HBV) immunization efforts could eliminate transmission of this infection and its related diseases worldwide, says an editorial in the *Journal of the American Medical Association*.

"On a global basis, (HBV) infection is a leading cause of morbidity and mortality due to acute hepatitis and the sequelae of chronic HBV infection, namely cirrhosis and primary hepatocellular carcinoma," says the editorial by Donald P. Francis, MD, DSc, of the Centers for Disease Control (CDC), Atlanta, and the California Department of Health Services, Berkeley, and the CDC's Harold S. Margolis, MD.

Although HBV-related diseases are most prevalent in Africa and Asia, "no part of the world is spared," the authors say. In the United States, for example, an estimated 300,000 people become infected with HBV annually, and direct medical costs for acute and chronic HBV-related diseases are more than \$1 million per day, the editorial notes.

"The good news is that the tools necessary to eliminate the transmission of HBV and its related diseases are at hand," the authors write. "Hepatitis B vaccines, which were developed more than 10 years ago, have been shown to be safe and effective in preventing HBV infection in adults, children, and infants born to HBV-infected mothers."

As evidence that HBV vaccine can reduce infection significantly, regardless of whether the primary period of transmission is in early childhood or among adults, Francis and Margolis cite a related study in this week's *JAMA*. That study, by Robert B. Wainwright, MD, of the Arctic Investigations Laboratory, Anchorage, AK, and colleagues, reports the virtual elimination of HBV transmission over a five-year period after widespread use of HBV vaccine in remote Eskimo villages.

In the five years following the vaccination demonstration project, which involved 1,630 Yupik Eskimos in southwest Alaska, the annual incidence of HBV infection decreased from 50 cases per 1,000 population before the trial to 0.45 per 1,000, the authors report.

"The reports by Wainwright et al and others also demonstrate that the duration of protection from HBV infection afforded by vaccine is long and that hepatitis B vaccines will prevent long-term HBV infections during the primary periods when an individual is at highest risk of acquiring these infections," the editorial says.

If all infants in populations with a high rate of perinatal HBV transmission received HBV vaccinations at birth, and if childhood immunization was implemented for infants in other parts of the world, "a worldwide cohort of persons protected from this long-term infection would be established," Francis and Margolis say.

"The elimination of HBV transmission is a sizable undertaking that requires a substantial commitment of effort and resources," they conclude. "The cost of hepatitis B vaccine has been declining rapidly on the world market, making the resources required much less than previously estimated. The savings in terms of human suffering and medical expenditures are considerable and provide a convincing argument for the adoption of this disease prevention strategy. So why not do it?"

JAMA April 28, 1989

OUTBREAK OF PENICILLIN-RESISTANT GONORRHEA

A report in the *Journal of the American Medical Association* describes a localized outbreak of penicillinase-producing *Neisseria gonorrhoeae*, (PPNG, or penicillin-resistant gonorrhea) that rapidly established itself in an inner-city population in King County, Washington. PPNG infections rose from 0.8 percent of reported gonorrhea cases in 1986 to 6.8 percent in the third quarter of 1987, then stabilized at 2.7 to 3.6 percent, say authors H. Hunter Handsfield, MD, of the Harborview Medical Center, Seattle, and colleagues. Of 268 PPNG isolates tested, 159 belonged to a single strain. As this strain spread, the authors say, the predominance of cases shifted from whites to blacks and from men to equal numbers of men and women; many of those affected were prostitutes, drug abusers, or their sexual partners. "These are priority target populations for behavioral intervention and other measures to control the spread of all sexually transmitted diseases, including human immunodeficiency virus infection," the authors say.

JAMA April 28, 1989

OBSESSIVE-COMPULSIVE DISORDER IN CHILDREN AND ADOLESCENTS

Obsessive-compulsive disorder (OCD) is a major disturbance of childhood, with a clinical picture strikingly similar to that seen in adults, a report in April's *Archives of General Psychiatry* says. Children with OCD often underreport their symptoms, "so a clinician must be particularly sensitive to the diagnosis," say authors Susan E. Swedo, MD, and colleagues at the National Institute of Mental Health, Bethesda, Md. The report involves 70 OCD patients, mean age 14, studied at the NIMH between 1977 and 1987. Boys outnumbered girls (the trend usually seen) and 25 percent of the subjects has a first-degree relative (mother, father, brother, sister) with OCD. Washing, grooming, and checking rituals and/or preoccupation with disease, danger and doubt accounted for the great majority of cases. The cause of this disorder is unclear, but the fixed content and style of symptoms, and their similarity among children never exposed to adult models of this behavior, suggest some kind of biological basis, the report says.

MEASLES PROTECTION IN HIV-INFECTED CHILDREN

A report in the *Journal of the American Medical Association* says children who are infected with human immunodeficiency virus (HIV) and are at risk for measles should be vaccinated against this disease because of its potentially fatal consequences. However, note authors Keith Krasinski, MD, and William Borkowsky, MD, of the New York University Medical Center, New York City, vaccination cannot guarantee measles immunity in these children. The authors say measles in four HIV-infected children they studied resulted in three severe pneumonias and one death, even though two of the children were immunized previously. Since the vaccine itself appeared to cause no adverse effects in the children studied, the authors urge immunization of children at risk "although the immunogenicity of measles vaccine in children infected with (HIV) is low and vaccine failure occurred." Due to the uncertainty about the vaccine's effectiveness, however, the research also recommends prophylactic use of immunoglobulin in HIV-infected youngsters exposed to measles.

JAMA May 5, 1989

MAMMOGRAPHY IN ASYMPTOMATIC WOMEN OVER AGE 40

Mammography is currently the most effective way of detecting early breast cancers, says an AMA Council on Scientific Affairs report published in the *Journal of the*

American Medical Association. There is growing evidence of the effectiveness of mammographic screening in reducing breast cancer mortality in women aged 40 to 49, although the data are not yet as strong as they are for women aged 50 and older, says the report. "Questions regarding age-specific, optimal screening intervals continue to be addressed, and as additional data are collected in (ongoing studies), more informed responses to such questions, including the comparative effectiveness of self-examination, physical examinations, and mammography, as well as const-effectiveness based on high false-positive rates, should be possible," the report. Until more data become available, the report says the AMA recommends annual screening mammograms and clinical breast exams in asymptomatic women aged 50 and older, and at one-to-two-year intervals in asymptomatic woman aged 40 to 49.

JAMA May 5, 1989

PRENATAL COCAINE EXPOSURE AND RESPIRATORY ABNORMALITIES

Infants exposed to cocaine prenatally appear to be at increased risk of abnormal cardiorespiratory patterns and have a higher rate of sudden infant death syndrome (SIDS) than do infants exposed to opiates, a study in May's *American Journal of Disease of Children, AJDC*, indicates. The study, by Ira J. Chasnoff, MD, of the Northwestern University Medical School, Chicago, and colleagues, reports a retrospectively determined SIDS rate of 15 percent in 66 infants exposed to cocaine in the womb, compared with 4 percent in infants prenatally exposed to opiates. The authors also prospectively studied cardiorespiratory pattern in 32 cocaine-and 18 methadone-exposed infants. Breathing abnormalities, including apnea, were seen more often in the cocaine-exposed infants. "Larger prospective studies will be necessary, however, to determine the pathophysiologic relationship between SIDS and prenatal drug exposure," the authors conclude.

ADRENAL IMPLANTATION FOR TREATMENT OF PARKINSON'S DISEASE

A study in May's *Archives of Neurology* calls for a controlled trial of adrenal tissue transplantation for treating Parkinson's disease. The authors, George S. Allen, MD, PhD, and colleagues at the Vanderbilt University Medical Center, Nashville, describe a pilot study involving 18 patients who underwent the transplant procedure, in which tissue from their adrenal medulla was placed into the dopamine-deficient part of the brain believed involved in Parkinson's. Four of 12 patients followed for one year showed "distinct improvement in the signs and symptoms of their disease," the authors say.

No distinct improvement was seen in the six other patients, who were an average of 20 years older and generally more severely affected. Four of these patients also experienced alterations in mental status lasting up to several months, the authors note. "However, we believe that the distinct and persistent improvement seen in some of the younger patients warrants the initiation of a well-designed, randomized and controlled trial... for the purpose of confirming these results and assessing the effect of the procedure on the natural progression of Parkinson's disease."

REDUCING URINARY INCONTINENCE IN THE ELDERLY

Urinary incontinence, common among the elderly and an epidemic in nursing homes, is ignored by many health professionals, even though it often can be treated successfully, say reports in the *Journal of the American Medical Association*.

One report describes the use of a behavioral therapy program to encourage continence in women nursing home residents. The other, from the National Institutes of Health's Consensus Development Panel on Urinary Incontinence in Adults, discusses the seriousness of the problem and the therapeutic options now available, and recommends steps to improve the treatment of incontinent adults.

Every incontinent person is entitled to evaluation and treatment when indicated, say authors John W. Rowe, MD, Mount Sinai School of Medicine, New York, and colleagues on the NIH panel. Contrary to common belief, most cases can be cured or improved with proper treatment. Of the 10 million Americans who are incontinent, more than half have had no evaluation or treatment, they report.

Failure to treat these patients is due to several factors, including underreporting by patients; underrecognition of the problem by health providers; lack of education of health providers regarding new research findings; inadequate staffing in long-term-care settings; and the persistent major gaps in our understanding of the causes of and the most effective treatments for the common forms of urinary incontinence, the authors report.

Incontinent patients should be made aware of the importance of reporting their symptoms to a health care professional, and should assert their right to proper assessment, diagnosis, and treatment, the panel recommends. Even frail nursing home residents often can have their problem improved or even cured, it says. The most common treatments include pelvic muscle exercises and other behavioral treatments, drug therapies, and a variety of surgical approaches. Urinary incontinence affects approximately 15 to 30 percent of the elderly residing in the community and at least half of all nursing home residents, the panel reports. The annual cost of managing the problem is conservatively estimated at \$10.3 billion. The psychosocial burden is also enormous—incontinence can limit or entirely prevent excursions

outside the home, social interactions with friends and family, and sexual activity.

Contrary to persistent myth, urinary incontinence is not a normal consequence of aging, although some age-related changes in lower urinary tract function may predispose older persons to incontinence from other damage to the urinary tract caused by injuries or illness, the report says.

"Many physicians fail to recognize the clinical impact of urinary incontinence in nursing homes, and very few nursing home residents with incontinence have had any type of diagnostic evaluation," say the authors. Instead, many incontinent nursing home residents are managed with indwelling catheters, which carry an increased risk of serious urinary tract infections.

Because medical and nursing education neglects the subject of incontinence, curriculum development is urgent, the panel says. Special emphasis should be placed on educating nurse's aides, due to the magnitude of the problems caused by incontinence in long-term-care settings, where inadequate staffing prevents proper treatment of incontinence and contributes to neglect of residents, it says.

The Consensus Development Conference on Urinary Incontinence in Adults was held last October by the NIH in conjunction with the National Institute of Diabetes and Digestive and Kidney Disease, the National Center for Nursing Research, the National Institute of Neurological Disorders and Stroke, and the Veterans Administration.

In an accompanying study, Teh-wei Hu, PhD, of the University of California, Berkeley, and colleagues describe a behavioral therapy program for treating urinary incontinence in female nursing home residents. One-hundred-thirty-three such women were assigned randomly to a 13-week behavior therapy program or to a control group that received usual care. While the number of incontinent episodes in the control group remained about the same at the end of the program, incontinence among the treated women was reduced an average of 0.6 episodes per day—a 26 percent reduction compared with the number prior to therapy.

The therapy involved checking treated patients hourly and prompting them to use the toilet. Patients were assisted to the toilet if necessary, and praised for successful toilet use. If the patient was found to be dry on the scheduled check, she was provided social reinforcement in the form of special attention, including time spent conversing or additional personal services.

During a six-month follow-up period, the treatment group maintained their improvement. The authors also report that some of the treated women developed stronger limbs as a result of daily use, participated more in nursing home activities, and showed improvements in their psychological well-being.

In an accompanying editorial, Joseph G. Ouslander, MD, of the UCLA School of Medicine, says that due to the enormous costs and adverse psychosocial consequences of urinary incontinence, the problem can no longer be ignored. "Allowing otherwise healthy incontinent people simply to go to the drug store and purchase adult diapers without a diagnostic evaluation or relegat-

ing incontinent nursing home residents to long-term indwelling catheterization with its attendant morbidity can no longer be justified."

Of key importance, he says, is finding effective methods of motivating nurses' aides to provide better care: "Usually less educated than other health professionals and paid minimal wages, nurses' aides are the key to providing humane and high-quality care to nursing home residents; aides provide more than 90 percent of the hands-on care in this setting."

JAMA May 12, 1989

STUDY: THYROID HORMONE USE IN ELDERLY COMMON, SOMETIMES INAPPROPRIATE

Use of thyroid hormone by the elderly is common but not always appropriate, says a study in the *Journal of the American Medical Association*.

In addition, some patients who take the medication for approved indications may not be taking adequate amounts, say the authors, Clark T. Sawin, MD, of the Tufts University School of Medicine, Boston, and colleagues. These findings suggest that physicians need to be aware that patients receiving thyroid therapy should be periodically re-evaluated, they say.

Thyroid therapy has never been proven beneficial in treating non-thyroid disorders such as obesity, elevated serum cholesterol, low blood pressure, hair loss, fatigue, and infertility, the authors write. Nevertheless, many patients appear to be taking thyroid hormones for these and other no-longer approved indications. "Inappropriate thyroid treatment is potentially hazardous, particularly in the elderly, who have more cardiovascular disease than younger adults." Thyroxine, the hormone produced by the thyroid gland, helps regulate the rate of many chemical reactions in the body. Currently appropriate reasons for thyroid therapy include benign goiter, hypothyroidism, and thyroid carcinoma, they report.

In their study of 2,575 older adults (average age 68.6), the authors found 6.9 percent (10 percent of women and 2.3 percent of men) were taking thyroid hormone. Twelve percent of these women were taking it for inappropriate indications, such as obesity or high serum cholesterol, while 29 percent of men on medication were inappropriately taking it to reduce elevated serum cholesterol, the report says. The authors suspected but could not show that an additional 7 percent of those taking thyroid hormones for possible hypothyroidism were also inappropriately using the therapy.

After follow-up averaging 6.9 years, the authors found that 58 percent of inappropriate users were still on the therapy. Inappropriate use was more often associated with the use of biologic preparations made from thyroid glands of animals rather than the synthetic thyroxine.

Underuse of thyroid hormone was also a problem. Of 95 patients with definite hypothyroidism, 35 (37 percent) at some point in the study were taking insufficient amounts of thyroid hormone to normalize their blood levels and 20 percent had insufficient therapy when last

seen. "The problem is probably due to a combination of poor compliance by patients and failure by physicians to assess the current needs of older patients, in whom symptoms are a relatively poor guide to the management of hypothyroidism," the authors report.

In an accompanying editorial, *JAMA* contributing editor David S. Cooper, MD, says synthetic thyroxine is clearly superior to the biologic preparations made from animal glands. Hormone levels in the animal gland preparations are not only unreliable, but these preparations can sometimes cause potentially harmful hyperthyroidism, he says. The biologic preparations contain another more potent thyroid hormone, called triiodothyronine, which, because it is made by other tissues in the body from thyroxine, is not needed. "Despite the superiority of synthetic thyroxine over the older and now obsolete biologic preparations, some 'nutritionists' and 'holistic health' practitioners continue to insist that the biologic preparations are more desirable because they are 'natural' or because they contain both (hormones)," Cooper writes. "Such disturbing and erroneous statements must not go unchallenged."

Cooper says it is surprising that some of the patients have been taking the medication for decades, for indications long considered inappropriate. "This points out the value of periodic reassessment of patients' medication regimens, not to mention the necessity for ongoing physician education," he concludes.

JAMA May 12, 1989

THOSE LUNG CANCERS NOT ATTRIBUTED TO SMOKING

There is overwhelming evidence linking smoking to lung cancer. But a letter in the *Journal of the American Medical Association* suggests that lung cancer not attributable to smoking is "one of the most common causes of cancer mortality" and seems to be especially important for blacks—particularly black men. The authors, Marvin A. Schneiderman, PhD, of the National Academy of Sciences, Washington, DC, and colleagues, used published data to calculate age adjusted death rates for non-smoking-attributable lung cancer in 1984. These rates were 9.3 per 100,000 for white men and 7.5 per 100,000 for white women. But the rates were 67 percent higher for black men (15.5 per 100,000) and 16 percent higher (8.8 per 100,000) for black women, they write. The cause of this differential is unclear. "This suggests the need for detailed study of lung cancers not associated with cigarette smoking, probably with large emphasis on differential environmental and occupational exposure, something to which the practicing, observing physician can contribute," the authors say.



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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

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Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

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Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

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Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

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Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

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These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should be abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

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Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

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VASOTEC

(ENALAPRIL MALEATE) MSD

Contraindications: VASOTEC® (Enalapril Maleate, MSO) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See PRECAUTIONS.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: **Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSO) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of 14 C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298/ patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostatic hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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